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## Original Communications

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### RESPONSES OF THE HUMAN POST-PARTUM UTERUS TO POSTERIOR PITUITARY EXTRACTS\*

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#### INTRODUCTION

**O**LIVER and Schafer<sup>1</sup> (1894) demonstrated that a preparation of the posterior pituitary gland caused an elevation of blood pressure. Dale<sup>2</sup> (1906) and Blair-Bell and Hicks<sup>3</sup> (1909) demonstrated that an oxytocic effect could be produced by an extract of the posterior pituitary gland. Shortly thereafter, posterior pituitary preparations were introduced as oxytocic drugs for clinical use. Kamm and his associates<sup>4</sup> (1928) claimed an almost complete separation of the oxytocic and pressor principles from pituitary extract and made these two factors available for physiologic and pharmacologic study and for clinical use. The oxytocic fraction was called pitocin and the pressor fraction, pitressin.

A review of the literature<sup>5-14</sup> revealed that very few investigators have studied the responses of the uterus of the laboratory animal to these substances in the immediate post-partum period. Many clinical investigators advocate the use of posterior pituitary extracts to control post-partum bleeding, but only a few have recorded kymographic tracings of the reactions of the human post-partum uterus to these preparations. Bourne and Burn<sup>15</sup> recorded uterine activity by means of a hydrostatic bag inserted 8 cm. above the cervical os in a patient during labor. They found that pitressin, even in large doses, produced no oxytocic effect while pitocin caused increased and sustained activity. Adair and Davis<sup>16</sup> administered pituitrin, pitocin, and pitressin intravenously to women immediately post partum and recorded the uterine activity by means of an intrauterine bag. Their tracings indicated that

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there was no essential difference in the effect of these three preparations on the human post-partum uterus. As pointed out by Weinstein and Friedman,<sup>17</sup> Adair and Davis did not investigate the possibility that the dose of pitressin administered might contain sufficient amounts of the oxytocic principle to produce a response in the extremely sensitive post-partum uterus. Moir<sup>18</sup> demonstrated by kymographic tracings that pituitary extracts injected subcutaneously produced a rapid and definite oxytocic action in the post-partum patient.

Commercial extracts are prepared from the posterior pituitary gland of the ox and are standardized briefly as follows: The oxytocic fraction is assayed *in vitro* on muscle strips from the uterus of the virgin guinea pig. The vasopressor fraction is assayed *in vivo* by its effectiveness in elevating the blood pressure when injected intravenously into an anesthetized dog. One milligram of the International Standard Powder represents about 7 mg. of fresh posterior lobe (ox) and contains 2 International Units of the oxytocic substance (Van Dyke, 1936).<sup>19</sup> There is no international pressor unit. Parke, Davis and Company have adopted a method of comparing the pressor effect of posterior pituitary extracts with known standards. This activity has been expressed in pressor units.

The amounts of the oxytocic and pressor factors in the Parke, Davis and Company extracts are as follows (Kamm).<sup>20</sup>

AMOUNT	INTERNATIONAL OXYTOCIC UNITS	PRESSOR UNITS
Pituitrin 1 c.c.	10	5-10
Pitocin 1 c.c.	10	Traces
Pitressin 1 c.c.	Traces	10 or 20

#### METHODS

Normal post-partum patients were selected on the sixth to ninth days after delivery. Following the method of Adair and Davis, a 10 c.c. Hagner bag was inserted, under sterile precautions, into the uterine cavity and was attached by a water system to a recording mercury manometer. Kymographic tracings of uterine activity were recorded when posterior pituitary extracts were injected either intravenously or subcutaneously. This method of study has been carried out on 200 patients and no deleterious effects have been noted. This paper deals only with the results obtained from the intravenous injection of posterior pituitary substances.

Solutions of pituitrin, pitocin, and pitressin were used. There was considerable individual variation in the responses of different patients to similar doses of the same drug. To rule out this individual variability, it was deemed necessary to compare the oxytocic effect of each of the three posterior pituitary extracts on each patient. The sequence of administration was varied to avoid any induced tolerance or sensitivity due to a previously administered drug. Twelve patients were studied in this manner (Table I). The dose was 0.3 c.c. in each instance because this was found to be the maximum amount of pitressin (3 pressor units) that could be given intravenously without causing undue pressor symptoms. Kymograph tracings were made for fifteen to thirty minutes prior to the injection of a preparation to determine the character of any spontaneous uterine activity. The interval between injections varied from thirty to sixty minutes and at least ten minutes was allowed

TABLE I. SEQUENCE OF ADMINISTRATION OF THE POSTERIOR PITUITARY EXTRACTS

NO. OF PATIENTS	FIRST DRUG	SECOND DRUG	THIRD DRUG
2	Pitocin	Pitressin	Pituitrin
2	Pitocin	Pituitrin	Pitressin
2	Pitressin	Pitocin	Pituitrin
2	Pitressin	Pituitrin	Pitocin
2	Pituitrin	Pitocin	Pitressin
2	Pituitrin	Pitressin	Pitocin

to intervene between the cessation of activity induced by one preparation and the injection of the subsequent posterior pituitary extract.

Representative tracings of the responses of 5 patients in this group are shown in Fig. 1. There was very little spontaneous uterine activity preceding the first injection in any of these patients. In every instance the initial contraction appeared within ten to twenty seconds after the drug was injected. Individual variations of the responses occurred, but the general characteristics of the tracings were quite similar.

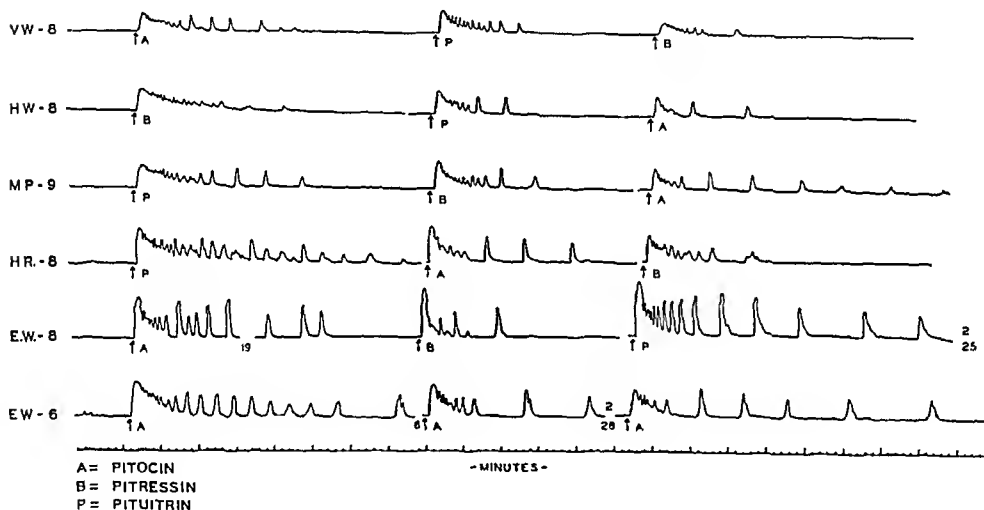


Fig. 1.—Kymograph tracings showing uterine responses to the intravenous administration of pitocin, pitressin, and pituitrin. The dose was 0.3 c.c. in each instance. The tracings have been arranged so that times of injection coincide on the time scale. The legend at the left of each tracing indicates the patient's initials and the day post partum. The numbers below the curve show the interval of time in minutes not shown on the tracing; those above the curve show the number of contractions during this interval. E.W.6 received three repeated injections of pitocin. E.W.6 and E.W.8 are different patients.

An analysis of the characteristics of these tracings further confirmed the similarity of the responses. The average values for the characteristics of the responses of all 12 patients are given in Table II. The average height of the initial contraction, the number of contractions during the first ten minutes, and the duration of the tonus were quite comparable for pitocin, pitressin, and pituitrin. Pitressin appeared to have a somewhat shorter effect.

These same characteristics were averaged according to the sequence of administration of the three preparations as shown in Table III. (The sequence is shown in Table I.) There was a decrease in the number of contractions in the first ten minutes and a decrease in the duration of tonus following the second and third drugs. These figures indicated a nonspecific decreased response to the second and

third drugs. To determine whether the diminished reaction would occur if the same drug were given repeatedly, three successive doses of pitocin were administered to a patient (E. W., 6 Fig. 1). The decreased reaction, especially to the second injection was quite marked. The fact that oxytocic activity of pitressin appeared so much like that of pitocin suggested two possibilities: first, that the human post-partum uterus may be so sensitive to posterior pituitary substances that it responds to the small fraction of the oxytocic substance in pitressin; or second, that there may be a marked species difference in sensitivity to these drugs. If the response of the human uterus were due to the small fraction of oxytocic substance present in pitressin, then it would be possible by equivalent quantitative dilutions of pitocin and pitressin, to find a dilution level at which pitocin would evoke a uterine response but at which level pitressin would not be effective. Dilution studies were made to test this possibility.

Table II. AVERAGE VALUES FOR THE CHARACTERISTICS OF THE UTERINE RESPONSES TO THE INTRAVENOUS ADMINISTRATION OF 0.3 C.C. OF PITUITRIN, PITOCIN, AND PITRESSIN

DRUG	NO. OF CASES	INT. INITIAL CONTRACTION MM.	CONTRACTIONS 1ST 10 MIN.	DURATION OF TONUS MIN.	TOTAL DURATION OF EFFECT MIN.
Pituitrin	12	27.5	12.3	6.6	31.5
Pitocin	12	28.1	10.3	4.8	35.1
Pitressin	12	28.9	12.6	5.8	20.0

TABLE III. THE AVERAGE VALUES FOR THE CHARACTERISTICS OF THE UTERINE RESPONSES ACCORDING TO SEQUENCE OF THE INTRAVENOUS ADMINISTRATION OF 0.3 C.C. OF PITUITRIN, PITOCIN, AND PITRESSIN

DRUG	NO. OF CASES	INT. INITIAL CONTRACTION MM.	CONTRACTIONS 1ST 10 MIN.	DURATION OF TONUS MIN.	TOTAL DURATION OF EFFECT MIN.
First drug	12	29.9	15.0	7.6	33.1
Second drug	12	29.4	10.7	5.0	22.2
Third drug	12	25.2	9.5	4.6	31.3

#### DILUTION STUDIES OF PITOCIN AND PITRESSIN

Especially assayed preparations of pitocin and pitressin were employed. The pitocin contained 10 International Oxytocic Units and 0.4 pressor units per c.c.; while each cubic centimeter of pitressin contained 0.4 International Oxytocic Units and 10 pressor units. These extracts were diluted with sterile normal saline solution in a range from 1:10 to 1:1,000. These preparations were given intravenously to 60 post-partum patients selected in the same manner as in the first part of the study.

In the first group, injections of 1 c.c. of equivalent dilutions of pitocin and pitressin were given to the same patient at approximately thirty-minute intervals, at least ten minutes elapsing between the cessation of activity caused by the preceding drug and the administration of the succeeding preparations. Again the sequence of treatment was varied to avoid any induced tolerance of sensitivity due to the previously injected drug. It is obvious from the tracings (Fig. 2) that almost identical effects were produced by comparable dilutions of pitocin and pitressin despite their wide difference in oxytocic values. Both preparations were usually ineffective at dilutions greater than 1:100.

A second group of patients were given dilutions of pitocin and pitressin, representing equivalent oxytocic activity. Although the oxytocic values were equivalent by the guinea pig assay method, the reactions of the human post-partum uterus were decidedly different (Fig. 3). Uniformly, the pitressin elicited a greater response

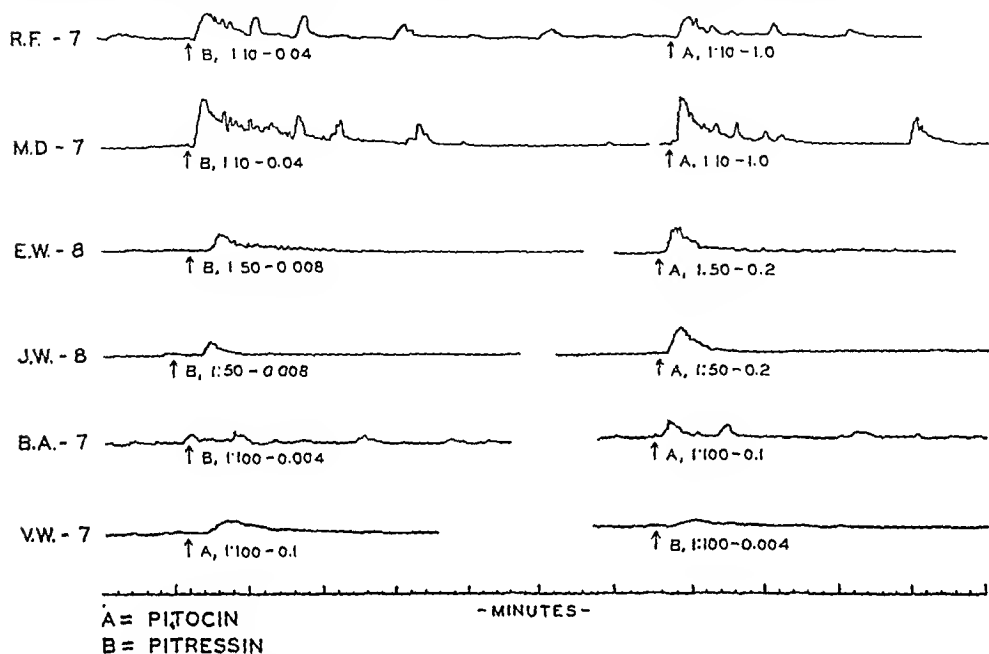


Fig. 2.—Kymograph tracings showing the responses to comparable dilutions of pitocin and pitressin. According to the guinea pig assay, the oxytocic value of pitocin was 25 times more potent than pitressin. The legend under each curve indicates: posterior pituitary extract, dilution of the preparation, the oxytocic potency in International Units. The dose was 1.0 c.c. intravenously, in each instance.

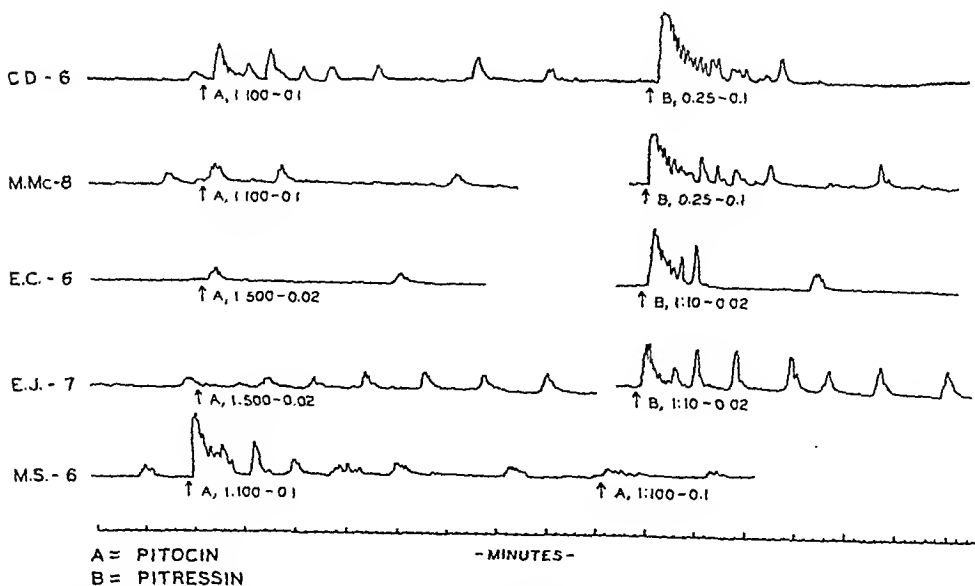


Fig. 3.—Kymograph tracings showing responses of the human post-partum uterus to intravenous doses of pitocin and pitressin which were equivalent in oxytocic values according to guinea pig assay. The legend under each curve indicates: posterior pituitary extract, the dilution of the preparation, the oxytocic potency in International Units. The dose was 1.0 c.c. in each instance, except in the second administration to C.D. 6 and M.Mc. 8, in which the dose was 0.25 c.c. of the undiluted preparation of pitressin.

than did pitocin. The greater response to pitressin when given as the second drug is more significant in view of the fact that results with large doses have shown that the second and third injections were not as effective as the first. The diminished effectiveness of a second injection was demonstrated when two small doses of pitocin were given to the same patient (shown in the tracing of M. S. -6, Fig. 3).

Table IV shows the positive, questionable, and negative uterine reactions in 96 different administrations of the various dilutions of pitocin and pitressin in 60 post-partum patients. The distribution of the responses for pitressin and pitocin could almost be superimposed, showing that similar dilutions exert similar oxytocic effects despite the wide differences in their oxytocic potency as expressed in International Units. According to the guinea pig assays, the pitocin was 25 times more potent as an oxytocic than pitressin, yet, in the human, similar dilutions of pitocin and pitressin were found to evoke similar uterine responses. The minimal effective dose of pitocin and pitressin was found to be about 1 c.c. of a 1:100 dilution of either extract.

An analysis of the characteristics of uterine reactions to the various dilutions of pitocin and pitressin is given in Table V. The height of the initial contraction varies. In some instances the greater dilutions stimulated a greater initial contraction, but all were less than those which followed the large doses. The number of contractions in the first ten minutes and the duration of tonus were similar in all the dilutions as well as in the large doses. These two characteristics seem to be typical manifestations which occur when the uterus responds to the posterior pituitary extracts, regardless of the dose administered. Large doses of pitocin produced a longer total duration of effect than did small doses. Conversely, there was a gradual increase in total duration of effect with higher dilutions of pitressin; the oxytocic effects of the small doses of pitressin were consistently longer in duration than for the larger doses.

TABLE IV. SHOWING THE POSITIVE, QUESTIONABLE, AND NEGATIVE UTERINE RESPONSES IN 96 DIFFERENT INTRAVENOUS ADMINISTRATIONS OF THE VARIOUS DILUTIONS OF PITOCIN AND PITRESSIN IN 60 POST-PARTUM PATIENTS. THE DOSE WAS 1.00 C.C. IN EACH INSTANCE

DILUTION	INT. UNITS OXYTOCIC	PITOCIN			INT. UNITS OXYTOCIC	PITRESSIN		
		+	±	-		+	±	-
1:10	1.0	8			0.04	11	1	
1:50	0.2	8	2	1	0.008	3		3
1:100	0.1	12	2	5	0.004	9	3	5
1:500	0.02	1	1	9	0.0008			3
1:1000	0.01			4	0.0004		1	4

TABLE V. AVERAGE VALUES FOR THE CHARACTERISTICS OF THE UTERINE RESPONSES TO INTRAVENOUS ADMINISTRATION OF 0.3 C.C. OF UNDILUTED (TABLE II) AND 0.1 C.C. OF DILUTED PITOCIN AND PITRESSIN (THE DILUTION FIGURES ARE THE AVERAGE OF THE POSITIVE RESPONSES IN TABLE IV)

DILUTION	HT. INITIAL CONTRACTION MM.		NUMBER CONTRACTIONS 1ST 10 MIN.		DURATION OF TONUS MIN.		TOTAL DURATION OF EFFECT MIN.	
	A*	B	A	B	A	B	A	B
Undiluted	28.1	28.9	10.3	12.6	4.8	5.8	35.1	20.0
1:10	15.0	21.2	9.7	14.9	4.9	7.3	22.7	33.0
1:50	15.0	9.7	9.6	13.0	3.5	3.5	15.2	31.0
1:100	20.0	13.0	10.6	12.0	3.8	5.0	26.3	37.9

\*A, Pitocin; B, pitressin.

With the exception of the difference noted in the total duration of effect, there was no marked difference in the oxytocic activity of the equivalent dilutions of pitocin and pitressin. Therefore, the oxytocic effect of large doses (0.3 c.c.) of pitressin on the human uterus is not due to the small amount of the oxytocic factor as determined by guinea pig assay, but is due to the fact that pitressin itself is oxytocic in the human being. The explanation of the contrasting results obtained when these drugs are administered to the post-partum human patient and to the laboratory animal must be based on a species difference in response to pitressin.

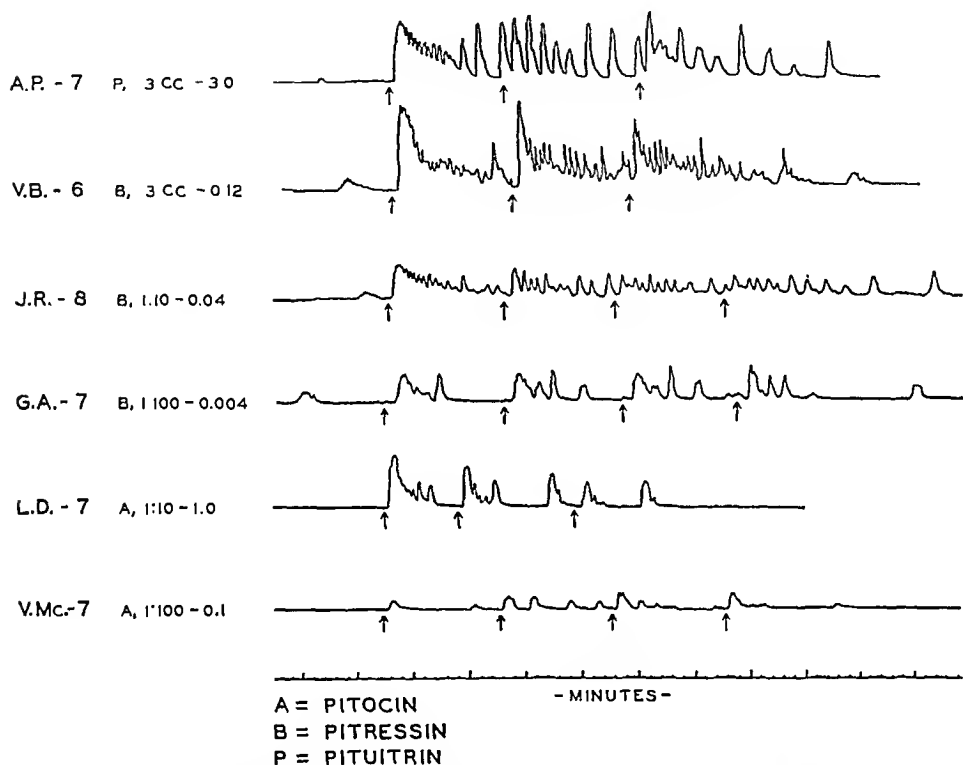


Fig. 4.—Kymograph tracings showing responses to repeated intravenous doses of pitocin, pitressin, and pituitrin. Legends at the left of the curves indicate in order: initials of patients, day post partum, posterior pituitary extract, amount of undiluted preparation or specific dilution, oxytocic potency of the extract in International Units. In the first two patients, 0.3 c.c. of the undiluted preparations was used, while in the remainder, the dose was 1.0 c.c. of the diluted extract as noted in the figure.

Further manifestations of species differences are also evident in this study. In experiments on the laboratory animals, it was found necessary to use a uterus that exhibited spontaneous or induced rhythmic activity in order to carry out studies with posterior pituitary extracts. In the post-partum patients many of the uteri showed no evidence of activity after insertion of the bag, yet an active response to the extracts was obtained. Most of the results on those patients with spontaneous rhythmic uterine contractions were not clear-cut and were difficult to interpret.

#### REPEATED INTRAVENOUS INJECTIONS OF POSTERIOR PITUITARY EXTRACTS

Weinstein and Friedman showed that large doses of pitressin had an inhibiting effect on spontaneous or induced uterine activity in rabbits.



During this period of inhibition the uterus of the rabbit would not respond to subsequent doses of pitocin. They also found that after the initial oxytocic effect of pituitrin, there occurred a state of uterine inactivity which was due to the pitressin fraction present in the pituitrin. In our experiments, large doses of pituitrin and pitressin stimulated contractions of the human uterus, and there was no evidence of an inhibition of uterine activity. Furthermore, large doses of pituitrin or pitressin repeated every ten minutes caused definite and sustained uterine activity following each injection (see Fig. 4, first 2 tracings). These two tracings also demonstrated a decrease in response to the subsequent injections of large doses of any of the three pituitary extracts. There was no cumulative effect or increased sensitivity when these substances were given at frequent intervals.

Weinstein and Friedman found that small doses of pitressin, while producing no active inhibition of spontaneous uterine activity in the rabbit, did render the uterus refractory for a period of time to subsequent doses of pitocin. In the present study repeated injections of dilutions of pitocin and pitressin were administered to a number of patients (see Fig. 4, last 4 tracings). On each occasion the uterus responded to small doses of pitressin in a manner similar to that of pitocin. Amounts of pitressin less than the minimal effective doses produced no change in spontaneous or induced uterine activity. There was no evidence that these small amounts produced a state of tolerance which rendered the uterus refractory to subsequent doses of pitocin.

#### DISCUSSION

Factual observations regarding the pressor effects of the various dilutions of the posterior pituitary extracts used in this study were not recorded. The impressions gained during the progress of the work suggest that the pressor factor has been largely separated from pitocin. Only a few of the patients given large doses of pitocin had pressor symptoms. Patients given smaller doses of pitocin never experienced any pressor manifestations whereas those receiving comparable doses of pitressin frequently complained of pressor effects.

From assay studies on a large number of patients, it has been concluded that 1 c.c. of a 1:100 dilution of either pitocin or pitressin is the minimal dose which will cause a definite oxytocic response in the majority of cases. On this basis, a human oxytocic unit might be defined as the smallest amount of posterior pituitary extract given intravenously which produces a definite effect as recorded by an intrauterine bag in the human uterus on the sixth to the ninth post-partum day. In our experience this human unit is approximately 0.01 c.c. of pituitrin, pitocin, or pitressin (Parke, Davis) and is equivalent to 0.1 International Oxytocic Unit.

There was no appreciable difference between the uterine responses on the sixth and the ninth days post partum to large intravenous doses (0.3 c.c.) of the three posterior pituitary extracts studied. The characteristics of our kymograph tracings were very comparable to those obtained by

Adair and Davis in their studies on the post-partum uterus in the first few hours following delivery. Thus, we believe that the results obtained in this investigation may be applied to patients in the immediate post-partum state.

#### CLINICAL APPLICATION

This study would indicate that when posterior pituitary extracts are given intravenously to combat post-partum hemorrhage, the initial tetanic contraction of the uterus may be anticipated within ten to twenty seconds. While uteri vary in their degree of response to posterior pituitary extracts, the induced activity usually lasts for a period of about thirty minutes. Subsequent intravenous doses are less effective than the first. Failure of the post-partum uterus to contract after the intravenous administration of 0.3 c.e. of posterior pituitary extract should be regarded as a grave sign and preparations for more active treatment of the uterine atony should be made without delay. It has been our experience that patients who fail to respond to the intravenous injections of posterior pituitary extracts usually require intrauterine packing to control post-partum bleeding.

Pitocin rather than pituitrin should be employed in patients with potential or actual toxemia of pregnancy to minimize the possibility of "pituitary shock," which may be caused by the pressor factor present in pituitrin.

#### CONCLUSIONS

1. Large intravenous doses (0.3 c.e.) of pituitrin, pitocin, and pitressin evoke similar oxytocic effects in the human post-partum uterus.

2. Equivalent dilutions of pitocin and pitressin, administered intravenously, produce equivalent oxytocic effects in the human post-partum uterus in spite of the wide variation in oxytocic values as assayed on the strips from the uterus of the virgin guinea pig.

3. Dilutions of pitocin and pitressin representing equivalent oxytocic activity by guinea pig assay method when given intravenously, are not equally effective in the human being.

4. The present methods of commercial assay do not give an index of the actual clinical oxytocic potency of pitressin.

5. There is no evidence that a tolerance develops in the human post-partum uterus following repeated intravenous injections of posterior pituitary preparations although there is usually a decreased response to repeated injections.

6. There is no inhibition of activity in the human post-partum uterus following injections of pituitrin or pitressin as has been described in laboratory animals.

7. The differences in the uterine responses of the post-partum patient and of the laboratory animal to posterior pituitary extracts are best explained as manifestations of a species difference.

8. A human oxytocic unit for posterior pituitary extracts has been defined.

The various preparations employed in this study were generously supplied by Parke, Davis and Co.

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## THE DIAGNOSTIC SIGNIFICANCE OF THE ENDOMETRIAL GLANDS IN EARLY PREGNANCY

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THE diagnosis of pregnancy from eurette material has generally rested upon the presence of either decidua vera or chorionic villi in the specimen removed. In this paper attention is called to the importance of recognizing a characteristic pattern of increased glandular activity in the endometrium. This picture has been found consistently and early in the cases reported. Although this is a small group, it suggests that the unusual secretory activity described below may occasionally prove to be a reliable aid in the diagnosis of gestation. The significance of this finding lies in the fact that it may be the only diagnostic sign present. When biopsies were taken on seven of the patients, within six weeks from the last flow, neither the patient nor the doctor suspected pregnancy. In three of these seven specimens no decidua or villi were seen and the only indication of conception was found in the glands. In these three cases then, the diagnosis would have been missed if this pregnancy sign had not been recognized.

During the years 1935 to 1938, 1,500 endometrial biopsies have been prepared and examined in the Pathological Laboratory of the Massachusetts General Hospital.\*

In this series of 1,500 biopsies, taken for a variety of gynecologic conditions, all phases of both normal and abnormal menstrual cycles have been observed. Eleven of the biopsies in this series, however, have

\*The preparation of these slides was made possible through the interest and help of Dr. T. B. Mallory.

shown a certain similar and distinctly unusual pattern of secretion in the endometrial glands, and in 10 of these 11 cases an early pregnancy was confirmed by subsequent events. A description of the histology involved is presented first, followed by a summary of the 11 cases and finally, the single case in which pregnancy was not confirmed is presented in detail.

Most of the 1,500 biopsies were taken with a sharp-lipped retraction eurette described by Meigs.\* The tissue removed averages not more than 5 c. mm. in our hands and frequently less. Generally an attempt is made to scrape out tissue from the region of one or both cornua. The specimen is immediately fixed in Zenker's solution and paraffin sections are cut and stained with hematoxylin and eosin. We feel that such tissue, although small, gives a very satisfactory diagnosis of endometrial function. However, in the present series of 11 cases,

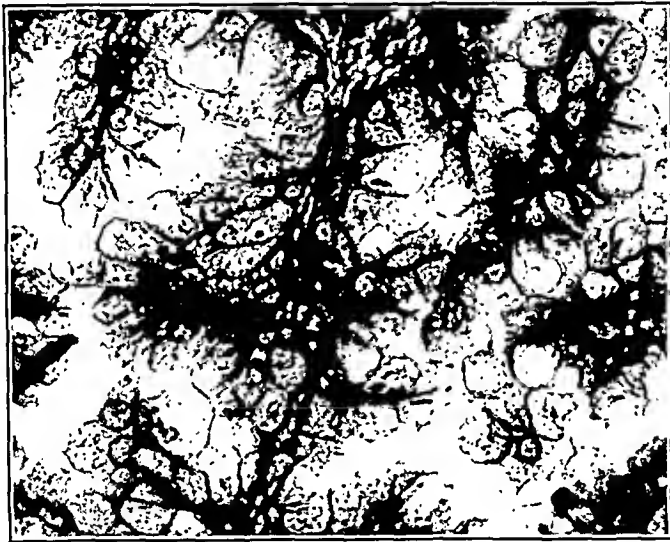


Fig. 1.—Case 10. Biopsy fifty days after onset of previous menses.

it is demonstrated that not infrequently such small pieces may be removed in early pregnancy without finding either decidual tissue or villi on microscopic study. It may be that the site of the biopsy was at a distance from implantation and that, in some of the early cases, the decidual response had not yet involved all of the functional endometrium. Possibly in other cases the superficial decidua-bearing layer was lost from the specimen in transfer. In any case, all eleven biopsies contained an adequate number of glands in the spongy layer showing unusual secretion to suggest a diagnosis of pregnancy.

Under low power, these glands are saw-toothed when cut longitudinally and star-shaped with many invaginations when cut across. In the spongy layer they lie crowded close together in early gestation and their general configuration is similar to that seen during the active luteal

\*In press.

phase of the menstrual cycle. The lumina may contain cellular debris but not usually sufficient to cause distention of the gland walls which, more often, lie in contact. It is only under high power that the details of differentiative cytology can be seen. The epithelial cells lining the glands are swollen, larger and higher columnar in type than at any time in the normal menstrual cycle (Fig. 1). This forces them to bulge

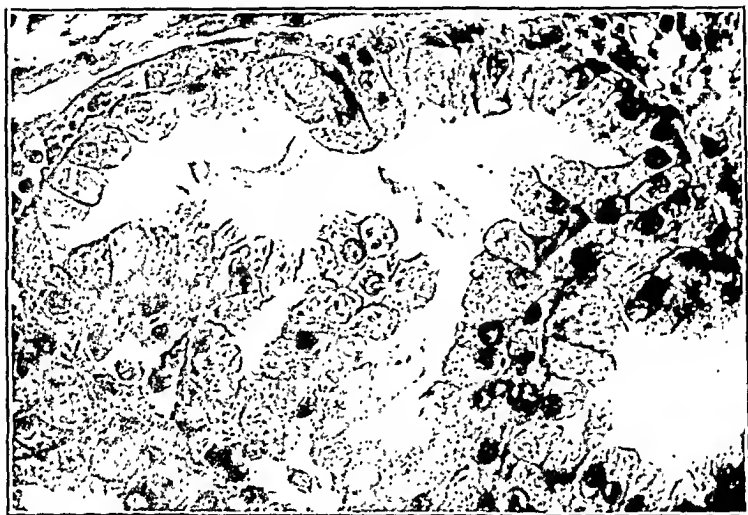


Fig. 2.—Case 4. Biopsy thirty days after onset of previous menses.

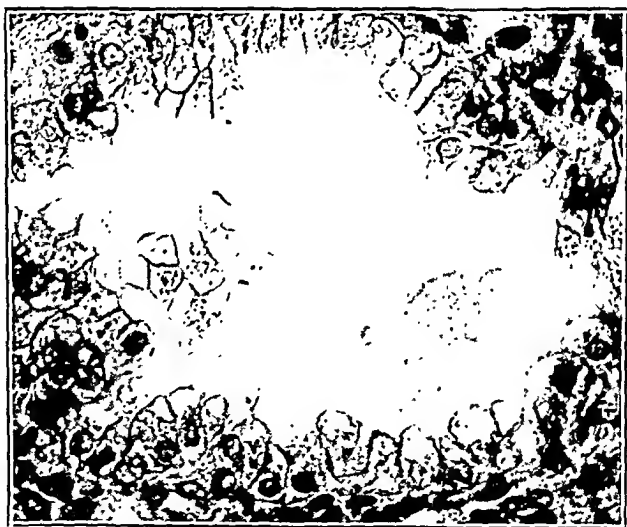


Fig. 3.—Case 7. Biopsy thirty-six days after onset of previous menses.

into the lumen like an exaggerated goblet cell (Fig. 2). They are filled with coarse, deep-staining granules, except at the luminal margin where these granules are absent and a fine reticular network can be made out (Fig. 3). Their free edge, ballooning out into the lumen, usually shows a clear-cut, sharp and distinct cell membrane (Fig. 4). The nuclei are round, light staining and near the basement membrane. There are no epithelial mitoses.

Table I summarizes the 11 cases out of 1,500 biopsies which showed this type of secretory activity. These cases are arranged chronologically from the earliest, taken twenty-five days after onset of the previous period to the latest removed sixty days after the menses. In the first eight, because of previous histories of irregular cycles, the presence of a pregnancy was not suspected at the time the biopsy was taken. The procedure was done in the clinic and the patients were allowed to go home. It is of interest that of these 8 cases where the pathological report gave

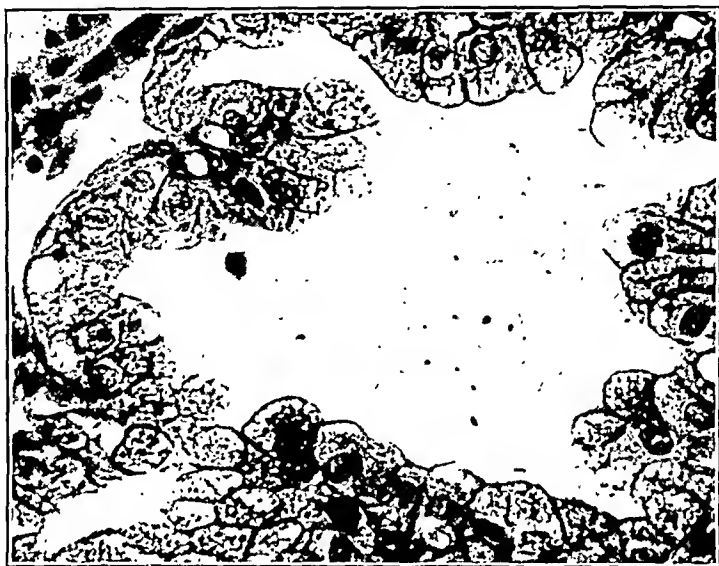


Fig. 4.—Case 5. Biopsy thirty-three days after onset of previous menses. Note the sharp distinct margin.



Fig. 5.—Case 8. Biopsy forty-two days after onset of previous menses. See case report.

the first positive evidence of conception and none but routine precautions were used, there have been 4 full-term babies and 3 others have successfully passed the first trimester. The remaining one, Case 8, is reported in detail below. In the last 3 cases, pregnancy was definitely suspected and the biopsy was done to substantiate the diagnosis with the patient in the hospital. In Case 9, the patient was bleeding and a diagnosis of incomplete miscarriage seemed probable at the time the specimen was removed. In Cases 10 and 11, biopsies were taken as an incidental pre-

TABLE I. SUMMARY OF CASES

CASE	PATH. NO.	IN- CREASED GLANDU- LAR AC- TIVITY	DAYS AFTER LAST CATA- MENIA	DECIDUA VERA	CHORI- ONIC VILLI	SUBSEQUENT PROOF OF PREGNANCY
1	37-1404	+	25	+	0	Baby
2	35-5096	+	27	+	0	Baby
3	38-4397	+	27	+	0	Aschheim-Zondek positive one week later
4	36-4927	+	30	0	0	Baby
5	38-5374	+	33	0	0	Aschheim-Zondek positive two weeks later
6	36-4927	+	34	0	0	Baby
7	38-4997	+	36	+	0	Aschheim-Zondek positive one week later
8	38-5359	+	42	0	0	Probable miscarriage. (See case report)
9	37-5547	+	45	0	+	Incomplete miscarriage. Dilata- tion and curettage
10	36-2614	+	50	0	0	Tubal pregnancy; salpingectomy
11	38-2189	+	60	+	0	Tubal pregnancy; salpingectomy

liminary to an operation for tubal pregnancy. It is clear then that in these cases endometrial biopsies taken early in pregnancy did not, as a rule, interfere with the course of gestation.

Decidua vera was encountered in only 5 slides and chorionic villi were found only once. In this group, then, the diagnostic significance of increased secretory activity is seen particularly in Cases 4, 5, 6, 8, and 10, where there was no other evidence of conception on a study of the microscopic section. In all the cases except Case 8 it was possible to corroborate this evidence either by a progression of the pregnancy, in Cases 1 to 7, or by operation in Cases 9 to 11.

CASE 8.—(Path. No. 38-5359.\*) A 39-year-old white woman, married four and one-half years, under treatment for sterility. Two years previously a dilatation and curettage had been done for a probable incomplete miscarriage. There had been no other pregnancies. Her periods were usually regular, but four to six days early, and lasted six days; occasionally a month would be skipped. From March, 1938 through August, periods were regular. Her menses from September 27 to October 1 was two weeks late. It was then decided to do weekly endometrial biopsies until her next flow to determine if normal ovulation were occurring. The first specimen was taken October 4 and the sixth and last November 7, although the patient had started to have a little bleeding by November 2 which did not stop until November 14. During this twelve-day flow she was perfectly well and did not notice passing clots or tissue. Subsequently, she had a normal flow twenty-nine days afterwards.

\*The author wishes to thank Dr. J. V. Meigs for his permission to use this case report.

In this case, 6 biopsies were taken approximately a week apart from the seventh to the forty-second day after onset of the September period. The last one showed an increased secretory activity in the glands suggesting early pregnancy (Fig. 5) but no decidua or villi. An Aschheim-Zondek test was not done.

It is possible to determine with reasonable accuracy how soon this characteristic glandular response occurs after ovulation from analysis of these six specimens. Biopsies 1, 2, and 3 showed normally developing proliferative endometrium. No. 4, on the twenty-eighth day of the cycle, was found to be in a typical early secretory phase, considered to be postovulatory. No. 5 showed normally active secretion and No. 6 taken on the forty-second day of the cycle but only two weeks after the first histologic evidence of ovulation, is seen to have the unusual pattern of gland activity described above.

It was concluded (A) that this patient occasionally ovulated late; in October, presumably around the twenty-fifth day of her cycle; (B) that the glandular response emphasized in this study occurs very early, within two weeks after fertilization (see also Table I, Cases 1, 2, and 3); and (C) that this patient had a complete miscarriage at home but failed to recognize the passage of the products of conception. It must be remembered, however, that the only evidence of gestation in this case is that the type of secretion in the endometrial glands is similar to that seen in the 10 other cases here reported of proved pregnancy.

#### DISCUSSION

In a previous report,<sup>1</sup> the unusually active appearance of secretion in the glands of the decidua vera was noted and contrasted with that seen during the height of the luteal phase of the normal cycle. In a later study of the duration of this response through pregnancy,<sup>2</sup> it was suggested that this increased activity might result from the added stimulus of the pregnancy urine (P. U.) hormone. Excretion of pregnancy urine hormone sufficient to give a positive Aschheim-Zondek test takes place consistently about five to six weeks from the last catamenia. There is evidence in at least 5 of the cases here reported (Cases 1, 2, 3, 4 and 8) that the characteristic glandular response to pregnancy is recognizable before the Aschheim-Zondek test usually becomes positive. It seems probable that increased secretion in the glands may reflect the earliest elaboration of this hormone and that this picture can be recognized before enough pregnancy urine substance is produced to spill over in detectable quantity in the urine.

#### SUMMARY AND CONCLUSIONS

1. Eleven cases are presented, showing an unusual picture of endometrial secretion.
2. Ten of these patients later proved to have been pregnant at the time the specimen was removed. The eleventh case is reported in detail.
3. Taking a biopsy by the method described did not inevitably interfere with the course of early gestation.
4. The characteristic glandular response here described represents an increase in function consistent with early pregnancy, and in these cases proved to be a reliable and valuable aid in the histologic diagnosis from endometrial biopsy specimens.

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- (1) *Sturgis, S. H., and Meigs, J. P.*: Am. J. Surg. 33: 369, 1936. (2) *Sturgis, S. H.*: Am. J. Obst. & Gynec. 35: 752, 1938.



# SPECIFIC "TOXEMIA," ESSENTIAL HYPERTENSION, AND GLOMERULONEPHRITIS ASSOCIATED WITH PREGNANCY

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IT IS now generally felt that the term "toxemia" of pregnancy is general, vague, and inaccurate. W. W. Herrick<sup>1</sup> says, "Such a loosely used and inclusive term as toxemia of pregnancy can no longer be accepted as precise or specific. It should be subjected to critical analysis, perhaps dissected until there is nothing left." Irving<sup>2</sup> states "The term toxemia is now regarded as of poor descriptive value, since no toxin has been isolated in eclampsia, nor is the blood of eclamptic patients more poisonous than that of other pregnant women. The word toxemia has long been used to explain the manifestation of a disease, the nature of which we did not understand."

A great deal of confusion exists in the classifications of the toxemias. Obstetric textbooks disagree in their outlines of the types of toxemias. Stander<sup>3</sup> and his co-workers have reported their concept of a group of toxemic patients showing "low reserve kidney." Herrick<sup>4</sup> and his associates state, "The milder types of late toxemia, vaguely called low reserve kidney, recurrent toxemia, or nephritis, in their follow-up and necropsy manifestations, seem to resemble eclampsia and pre-eclampsia in that their frequent results are general vascular disease with hypertension rather than nephritis. The differences between the severe and milder types of nonnephritic late toxemias are of degree, not of kind." Kellogg<sup>5</sup> appeals for the universally accepted classification. He divides his patients into two large groups, namely, (a) those presenting evidence of disease independent of pregnancy and applies the Vollhard and Fahr classification of the nephropathies, adding to this pyelonephritis; and (b) those conditions specific to pregnancy, i.e., pre-eclampsia Grades 1 and 2; and eclampsia.

We use the following classification suggested by William Goldring (Lectures on Nephritis and Hypertension, Edward Brothers, Ann Arbor, Mich., 1937):

- A. Specific toxemia of pregnancy.
  1. Without convulsions (pre-eclampsia)
  2. With convulsions (eclampsia)
- B. Essential hypertension (pre-existing)
- C. Glomerulonephritis (pre-existing)
- D. Combinations of pre-existing essential hypertension or glomerulonephritis with superimposed specific toxemia.

During the past five years, we have attempted at Bellevue Hospital (1) to classify or group these patients; (2) to standardize their ob-

stetric care, if possible; (3) to determine the immediate effects on the mother and offspring; and (4) to determine the remote effects on the mother.

We believe that the treatment can be fairly uniform but must remain empirical, since the exact etiology is unknown. This treatment consists of (1) rest in bed, (2) sedatives (when indicated); (3) bowel hygiene, (4) in the presence of edema, the use of hypertonic solutions, 50 per cent sucrose and 10 per cent magnesium sulphate intravenously; salt poor and normal protein intake; and restriction of fluid intake not to exceed urinary output. When termination of pregnancy is considered, a vaginal examination is done to determine the state of the lower uterine segment and possible disproportion.

#### OCCURRENCE OF "TOXEMIA"

Dieckmann<sup>6</sup> says, "Approximately 8 per cent of the patients delivered in a maternity hospital had toxemia." He further quotes other observers, e.g., "The incidence of the toxemias of pregnancy for the Cornell University Clinic is 15.6 per cent and for the Johns Hopkins Clinic, 9.4 per cent as reported by Stander; Washington University Clinic 3.8 per cent according to Schwarz and Wegener; and 6.7 per cent for the University of Chicago Clinic. A conservative estimate of the number of patients with toxemia of pregnancy in the United States each year would be 100,000."

Our clinical study includes all patients from October, 1933, to October, 1938. During this five-year period there were 7,897 deliveries at Bellevue Hospital. Of these, 262 patients were observed through 272 pregnancies, complicated by the so-called toxemias. This is an incidence of 3.4 per cent.

All patients upon discharge were either referred to the Nephritis and Hypertension Clinic at the College or a similar special hospital follow-up clinic which has been in existence for three years.

#### AVERAGE AGE, PARITY, SIZE OF HEART AND RETINAS IN TOXEMIA

The following briefly analyzes some of the chief characteristics noted in each group (Table I):

*A. Specific Toxemia.*—The majority, 184 patients, were seen through 189 specific toxemic attacks. This is 69 per cent of the whole series.

*1. Nonconvulsive:* One hundred and sixty patients seen through 165 pregnancies were of the nonconvulsive type. The average age was 27 years. Primiparas prevailed and made up 64 per cent of this group. The hearts were chiefly not enlarged. Those showing enlargement were mainly due to rheumatic heart disease. The retinas frequently revealed hypertensive vessel changes (i.e., thinning, spasm or acute branching of arterioles, or A-V compression), whereas papilledema and areas of degeneration and hemorrhage were only occasionally present. Wagener<sup>7</sup> studied the arterioles of the retina in toxemia of pregnancy and found "that usually the first visible sign is a narrowing of the arterioles of the retina which may affect any or all of the branches of the central arteries. This narrowing is often accompanied or followed by irregular constrictions of the lumen of the arterioles, usually first or most marked in the smaller nasal branches, which may vary in degree and situation from day to day. Later, as the narrowing and constrictions become more fixed, individual cotton-wool patches and hemorrhagic areas may appear in the retina, and finally diffuse retinitis of the albuminuric type may develop."

TABLE I\*

CLASSIFICATION NUMBER OF CASES		RECUR. NO.	AVERAGE AGE	PARITY		SIZE OF HEART		RETINAS					
				PRIMIP.	MULTIP.	NO. X-RAYED	E.H. NO.	NORMAL	H.V.C.	H.V.C. AND H.R.	H.V.C. AND P.E.	P.E.	H.V.C. AND H.R. AND P.E.
Specific "toxemia" 184	Non-convulsive 160	5	27	107	53	108	13	60	50	2	4	3	0
	Convulsive 24	0	27	12	12	12	0	6	5	0	4	0	1
Pre-existing essential hypertension 64	Un-complicated 10	0	36	0	10	7	6	2	5	0	0	0	0
	Superimposed N.C.S.T. 51	5	35	4	52	36	29	4	25	6	2	1	6
	Superimposed C.S.T. 3	0	32	0	3	3	2	-	1	1	-	-	1
Glomerulonephritis 4	Un-complicated 0	-	-	-	-	-	-	-	-	-	-	-	-
	Chronic diffuse with N.C.S.T. 3	0	23	1	2	3	1		2				1
	Acute diffuse 1	0	30	0	1	1	0		1				
Unclassified 10		0											
Total 262		10											

\*N.C.S.T., Nonconvulsive specific toxemia; C.S.T., Convulsive specific toxemia; E.H., Enlarged heart; N., Normal; H.V.C., Hypertensive vessel changes; H.R., Hypertensive retinopathy (exudate and hemorrhage); P.E., Papilledema.

2. *Convulsive*: There were 24 specific toxemias with convulsions. Their average age was 27. Fifty per cent were primiparas, showing no cardiac enlargement. Their retinas showed hypertensive vessel changes with a greater tendency to papilledema.

B. *Pre-existing Essential Hypertension*.—Sixty-four women seen through 69 attacks began their pregnancies with pre-existing essential hypertension. They were 25 per cent of all the toxemias.

1. *Uncomplicated*: Only 10 or about 15 per cent remained uncomplicated. Analysis of the latter showed that their average age was 36 and each patient had had many pregnancies. Almost all those x-rayed had enlarged hearts. The retinas chiefly revealed hypertensive vessel changes.

2. *Superimposed Nonconvulsive Toxemia*: Fifty-one patients seen through 56 pregnancies developed superimposed nonconvulsive specific toxemia upon pre-existing essential hypertension. Their average age was 35 years. There were four young primiparas. The others had had many pregnancies; one was a para xvii. Eighty per cent of those x-rayed showed enlarged hearts. Their retinas showed more marked hypertensive vessel changes with a greater tendency to hemorrhage, areas of degeneration and papilledema.

3. *Superimposed Convulsive Toxemia*: Three patients developed convulsive specific toxemia superimposed on pre-existing essential hypertension. Their average age

was 32. They were multiparas, 2 showing enlarged hearts. Their retinas revealed marked hypertensive vessel changes, papilledema, hemorrhage, and areas of degeneration.

*C. Glomerulonephritis.*—In the entire series, there were only 4 patients with glomerulonephritis; none of these women remained uncomplicated. This limited incidence concurs with Young<sup>8</sup> who, in discussing chronic nephritis complicating pregnancy, said, "During a period of six years, when all our toxemias have been subjected to an intensive study, we have not found, among several hundred cases, more than four or perhaps five such cases."

*1. Superimposed Specific Toxemia:* Of this group, three patients with pre-existing chronic diffuse glomerulonephritis developed superimposed specific toxemia. Their average age was 23 years. Two were multiparas and 1 was a primipara. Of the 2 multiparas, 1 had an enlarged heart. Both had hypertensive vessel changes and in addition, one showed hemorrhage and areas of degeneration in her retinas. The primiparous patient became pregnant about six months after an attack of acute diffuse glomerulonephritis. She had mild hypertension and albuminuria from the onset of pregnancy. She went to term and showed some increase in symptoms just before and during labor. Labor was medically induced and she spontaneously delivered a live child.

*2. Acute Diffuse, Initial Attack:* One patient at the onset of pregnancy developed acute diffuse glomerulonephritis following a sore throat. She was thirty years of age, a para ii with hematuria (by Addis Count), mild hypertension, proteinuria and generalized edema. Pregnancy was terminated by a therapeutic induction at three months.

*D. Unclassified.*—The 10 unclassified patients did not present sufficient criteria in early observation or because of no follow up for us to be able to place them in any known group.

#### LABOR, DELIVERY AND RESULTS TO MOTHER AND BABY (TABLE II)

*A. Specific "Toxemia."*—*1. Nonconvulsive:* Labor was chiefly spontaneous. There were only seven medical inductions and one bagging. We await spontaneous labor unless progression of the toxemia warrants induction. The latter is only attempted when the cervix is favorable. Ninety-four patients delivered spontaneously; 52 by operative means, such as forceps; and 18 by cesarean section. One woman died undelivered. There were 132 babies born alive; 42 were stillborn. Nine sets of twins were in this group; 4 mothers died.

*2. Convulsive:* Labor was chiefly spontaneous with only 2 medical inductions. Fifteen patients delivered of their own accord and 7 by forceps. The 2 sections will be analyzed later. There was 1 set of twins. Sixteen babies were born alive; 9 were stillborn. Four mothers died.

*B. Pre-Existing Essential Hypertension.*—*1. Uncomplicated:* Labor was chiefly spontaneous; 1 patient was induced by bagging. Three had cesarean sections and 7 delivered of their own accord. All mothers recovered and 4 babies were stillborn.

*2. Superimposed Nonconvulsive Toxemia:* Only 4 patients were induced medically. There were 11 cesarean sections; one of these was done post mortem. Forty-two delivered spontaneously and 3 by forceps. Twenty babies were stillborn and 1 mother died.

*3. Superimposed Convulsive Toxemia:* Two were delivered by elective cesarean section. One had spontaneous labor and was delivered by forceps. Two babies were born alive and 1 was stillborn. All mothers lived.

*C. Glomerulonephritis.*—*1. Superimposed Specific Toxemia:* The 2 multiparas had elective sections and although they recovered, their babies were stillborn.

#### OPERATIVE TERMINATION OF PREGNANCY AND LABOR (TABLE III)

Thirty-eight women had their pregnancies terminated by abdominal operation. One of these was a post-mortem cesarean. In 25, or 9 per cent, of the entire series,

TABLE II\*

CLASSIFICATION NO. OF PATIENTS		RECUR. NO.	LABOR				DELIVERY			RESULTS		
			SPONT.	INDUCED		NONE	SPONT.	OPER.	CESAREAN	BABY		MOTHER DEATHS
				MEDICAL	BAG					ALIVE	DEAD	
Specific "tox- emia" 184	Non-convulsive 160	5	147	7	1	10	94	52	18	132	42	4
	Convulsive 24	0	22	2	-	-	1 Undelivered			9 Twins		
Pre-exist- ing essential hyperten- sion 64	Un- complicated 10	0	6	0	1	3	7	0	3	6	4	0
	Superim- posed N.C.S.T. 51	5	42	4	0	10	42	3	11	36	20	1
	Superim- posed C.S.T. 3	0	1	0	0	2	0	1	2	2	1	0
Glomerulo- nephritis 4	Un- complicated 0											
	Chronic dif- fuse with N.C.S.T. 3	0	0	1	0	2	1	0	2	1	2	0
	Acute diffuse 1	0	0	0	0	1	D & C at 3 months			0	1	0
Unclassified	10	0	9	1	0	0	7	3	0	5	5	0
Total	262	10	227	15	2	28	166	67	38	198	84	9
							1 Undelivered					

\*N.C.S.T., Nonconvulsive specific toxemia; C.S.T., Convulsive specific toxemia.

the prime motivating factor for the operation was the "toxemia." This is in contrast with the average cesarean rate of 2.3 per cent at Bellevue Hospital done for all other obstetric conditions.

Of the 20 operations in the specific toxemic group, 10 were primarily performed for reasons other than the toxemia. Of the remaining 10, giving an incidence of 6 per cent, 4 patients had severe early toxemia and 6 had impending convulsions. The two listed under the convulsive group were done prior to the onset of this complication. It is our policy to treat the convulsive patients conservatively. A woman with abruptio placentae had a hysterectomy. There were 2 tubal sterilizations. There was one maternal death. This patient received gum acacia to combat shock. At this time, other deaths and severe reactions to gum acacia were noted on the service.<sup>9</sup>

Of the patients with pre-existing essential hypertension, 13, or 18 per cent, had their pregnancies terminated by the abdominal route because of toxemia. Nine had repeated toxemias. Two had severe attacks in the second trimester of pregnancy and two had impending convulsions. Ten were sterilized and one had a hysterectomy.

The 2 hysterotomies done in the nephritic group were indicated because of severe superimposed specific toxemia. Both had tubal sterilization. Their clinical course fitted into the picture described by Herrick and Tillman<sup>10</sup> who said, "With repeated

TABLE III. TERMINATION OF PREGNANCY BY ABDOMINAL OPERATION\*

CLASSIF. AND NO.	NO. OF OPER.	OTHER THAN TOX.		COR. NO.	% OPER. FOR TOX.	TOXEMIA INDICA- TIONS			TYPE OF OPER.		STERILIZATION	MAT. DEATHS
		PELVES, ETC.	ABRUPTIO PLACENTAE			SEVERE EARLY	IMPENDING CONVUL.	REPEATED TOX.	SECTION OR HYSTEROTOMY	HYSTEREC- TOMY		
N.C.S.T. 165	18	8	2	8	6	4	4	0	17	1	2	1
C.S.T. 24	2	Both done as non- convulsive		2	0	-	2	-	2	-	-	-
Essen. hyper. 69	15	-	2	13	18	2	2	9	14	1	10	-
Glom. neph. S.T. 3	2	-	-	2	66	-	2	-	2	-	2	-
Total tox. 272	37	8	4	25	9	6	10	9	35	2	14	1

\*Cesarean rate for all obstetric indications was 2.3 per cent; N.C.S.T., Nonconvulsive specific toxemia; C.S.T., Convulsive specific toxemia.

pregnancies, the renal breakdown appears earlier in pregnancy and is usually more serious and the result is less likely to be a living child. In a woman with nephritis, repeated pregnancy seems to encroach further on the factor of safety of the kidney and should be avoided."

Twenty-eight per cent of the remaining patients were delivered by forceps. This was done for prematurity, and in order to shorten the second stage, since toxemia tends to increase during this part of labor.

#### RECURRENCE OF TOXEMIA

*A. Specific Toxemia.*—This symptom complex shows a tendency to recur in subsequent pregnancies. Some patients ultimately remain with permanent hypertension after one of these attacks (Table V). While the period of follow-up in this study is not sufficiently long to answer the question, our impressions confirm the observations of others<sup>11</sup> that more than 50 per cent of toxemic women become permanently hypertensive. Many important questions arise, i.e., (1) What factors during an attack of specific toxemia will decide its recurrence or development of a permanent hypertensive state? Is it the clinical course of the disease in relation to (a) severity, (b) duration, (c) the period of gestation when symptoms began, or (d) is it the time required for the symptoms of the last attack to disappear, or (e) are there

TABLE IV. RECURRENCE OF SPECIFIC "TOXEMIA"

PARA	NO. OF CASES	TOXEMIA RECURRED NO.	PREVIOUS NORMAL PREGNANCIES NO.
ii	25	20	5
iii	11	3	8
iv	7	3	4
Total	43	26	17
Per cent		60	40

combinations of these factors? (2) Is it some underlying glandular or vascular defect with which these women are born or develop later on? In order to answer some of these questions, it is necessary to follow patients from an initial attack of specific toxemia between and through subsequent pregnancies and also to the necropsy table.

We have accumulated enough evidence to show that specific toxemia recurs. To date, it is premature for us to analyze the primiparas in this series during and between subsequent pregnancies. However, an analysis of those who had specific toxemia when they first presented themselves as para ii, iii, or iv shows that 60 per cent had at least one previous attack (Table IV).

*B. Pre-Existing Essential Hypertension.*—It was pointed out that multiparity is the rule in this group. About 75 per cent of these patients had at least one, more often many attacks of specific toxemia in previous pregnancies. Many of the remaining 25 per cent were delivered at home, having had no prenatal or interpregnancy supervision.

We selected 10 patients as a few of the group who were seen in their last pregnancy with pre-existing essential hypertension and specific toxemia (Table V). They

TABLE V\*

NAME	AGE L.P.	PARA									
		i	ii	iii	iv	v	vi				
C. B.	26	S.T.	ESS. S.T.	Essential hypertension							
E. M.	25	S.T.	S.T.	ESS. S.T.	Essential hypertension						
M. S.	36	O	O	S.T.	ESS. S.T.	Essential hypertension					
H. S.	35	O	O	S.T.	S.T.	ESS. S.T.	Essential hypertension				
F. C.	34	O	O	O	S.T.	ESS. S.T.	Essential hypertension				
L. C.	30	O	O	O	O	C.S.T.	ESS. S.T.	Essential hypertension			
A. W.	42	S.T.	O	O	S.T.	S.T.	ESS. S.T.	Essential hypertension			
M. K.	37	ESS. S.T.	ESS. S.T.	ESS. S.T.	ESS. S.T.	ESS. S.T. H.F.	Hypertensive H.D. with failure				
E. S.	42	O	O	O	S.T.	S.T.	ESS. S.T. H.F.	Hypertensive H.D. with failure			
C. F.	33	O	O	O	S.T.	ESS.	ESS.				
						[S.H.]					
						S.T.	S.T. S.H.				

\*ESS., Pre-existing essential hypertension; C.S.T., Convulsive specific toxemia; S.H., Subarachnoid hemorrhage; O., Normal pregnancy; H.F., Heart failure; S.T., Specific toxemia; L.P., Last Pregnancy; H.D., Heart Disease.

had attacks of specific toxemia in their previous pregnancies and entered their last one with permanent hypertension. They show some interesting facts, i.e., (1) One attack of specific toxemia may terminate in essential hypertension. (2) Attacks need not appear in successive pregnancies for the latter to occur. (3) It is interesting to note that 2 of these women developed marked congestive heart failure as a result of hypertensive heart disease. (4) Six out of these 10 women had permanent hypertension at the age of 35 or younger. There were 2 around 25 years of age. It has become evident in the past few years that the cardiovascularrenal

field is intimately connected with the toxemias of pregnancy in the active part of the disease, in subsequent pregnancy and in the intervals between pregnancies. Herrick and Tillman<sup>10</sup> made an extensive follow-up study of 594 posttoxic patients over a period of from one to twenty-two years or an average time of 5.6 years. Ninety women had died. Of these, 80 per cent were from causes within the cardiovascularrenal field. Irving<sup>2</sup> states, "There is considerable evidence that the disease (eclampsia) is vascular in nature and may best be explained on the basis of arteriolar spasm."

*C. Pre-Existing Glomerulonephritis.*—The 2 multiparous patients of this group had attacks of superimposed specific toxemias in all their previous pregnancies.

#### FETAL AND MATERNAL MORTALITY

*A. Fetal.*—Many factors contribute to the high fetal mortality rate. They are (1) prematurity, spontaneous or induced by the attendant, who is forced to terminate a pregnancy in order to lessen the immediate or remote hazards to the mother. (2) Immaturity, very often the fetus of a toxemic mother is smaller than that of a normal pregnancy of a like gestational period. (3) Intrauterine deaths, which often cause sudden improvement of the maternal status. The causes of these pregnancy deaths have theoretically been explained on the basis of possible placental changes; but as yet, no irrefutable evidence has been given of this phenomenon.

In this series, we did not differentiate nonviable from viable deaths but considered all fetuses dead if they did not live through the neonatal period.

The fetal death rate for all patients exclusive of toxemia during the period covered by this report was 3.6 per cent. In the toxemias, this rate was 30.8 per cent (Table VI).

TABLE VI. FETAL AND MATERNAL MORTALITY

FIVE YEARS ENDING OCTOBER, 1938	NO.	FETAL DEATHS		MATERNAL DEATHS	
		NO.	%	NO.	%
Nontoxic pregnancies	7625	281	3.6	25	0.32
"Toxemias"	272	84	30.8	9	2.8

*B. Maternal.*—The 3 outstanding causes of maternal mortality in the pregnant, parturient and post-partum periods are hemorrhage, sepsis, and the toxemias.

The uncorrected mortality rate among the toxemic patients was 2.8 per cent, compared with 0.32 for all other obstetric patients during this period.

#### SUMMARY

1. A workable classification for the so-called toxemias of pregnancy has been presented.

2. The dangers of toxemia are immediate and remote. If the condition progresses notwithstanding conservative medical treatment, pregnancy should be terminated.

3. The frequency with which essential hypertension follows toxemia of pregnancy has caused growing concern. While toxemia may actually induce persistent hypertension, it is possible that the pregnancy merely makes evident a latent hypertensive state. It is incumbent upon obstetricians to recognize that such a state may supervene. Therefore, a decision must be arrived at cautiously when judging the advisability of future pregnancies following one complicated by toxemia.

4. The imminent and future dangers of a pregnancy complicated by pre-existing essential hypertension should be discussed with the family. If the patient has living children, that pregnancy should be terminated and future ones avoided. Not infrequently, the method of choice is



hysterotomy with tubal sterilization. Fifteen out of 69 such pregnancies were terminated by abdominal operation. Ten women had tubal sterilizations.

5. Pre-existing glomerulonephritis is rare during pregnancy. It usually becomes complicated by specific toxemia.

6. The second stage of labor should be shortened by simple forceps delivery in order to prevent cerebral injuries in premature births and to forestall progression of the toxemic state.

7. The maternal mortality rate is high, the uncorrected rate in our series was 2.8 per cent.

8. There was a total fetal mortality rate of 30.8 per cent.

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### CONGESTIVE HEART FAILURE IN PREGNANCY

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SINCE the publication of Sir James Mackenzie's<sup>1</sup> book, *Heart Disease and Pregnancy*, a growing interest has developed in this subject. A large number of such patients are observed annually at the Woman's Clinic of the New York Hospital. The nature of their heart disease and the results of its management in a special cardiac clinic were reported in 1937 by Stander and Kuder.<sup>2</sup> While most of them experienced no cardiac difficulty during pregnancy, the maternal mortality of the group was twice as great as the general maternity mortality of the clinic and accounted for 10 per cent of the obstetric deaths. Since the report by Stander and Kuder, many more cardiac patients have been observed at the Woman's Clinic of the New York Hospital, and considerable information has accumulated concerning them. For the present report, information relating to those patients who developed cardiac failure associated with pregnancy has been analyzed.

#### RESULTS

Among 22,837 obstetric patients delivered in the last six and a half years, there were 620 with organic heart disease. Only 26 of these patients developed physical signs of congestion of the lungs or abdominal viscera associated with pregnancy. Heart failure thus occurred in less than 0.1 per cent of all pregnant patients and in approximately 4 per cent of all cardiac patients.

All degrees of congestive heart failure were found among the 26 patients studied, and details relating to its manifestations and course are recorded in Table I. The month of pregnancy at which each patient was first seen in heart failure is listed in column two, and when more than one attack occurred the month of each attack of failure is shown. The degree of pulmonary and hepatic congestion and edema has been recorded in columns three, four, and five on the arbitrary basis of + to +++, acute pulmonary edema being considered +++ pulmonary congestion. The type of delivery is also shown in this table. Forceps deliveries are included under spontaneous deliveries. The last column gives the latest follow-up of the case, using the functional classification 1, 2A, 2B, and 3 of the American Heart Association.

When the findings were tabulated in this way they fell into four distinct groups.

TABLE I. MANIFESTATIONS AND COURSE OF HEART FAILURE\*

CASE	MONTH	MANIFESTATIONS			DELIVERY	REMARKS
		LUNG	LIVER	EDEMA		
Group I						
1	3	+	+	+	Section	2A, 18 mo. later
2	4	+	0	+	Section at 5 mo.	Not seen since discharge
3	5	+	0	0	Spontaneous	2A, 7 yr. later; pregnant again
4	5	++	0	+	Section	2A, 4 yr. later
5	5	+	0	0	Section	2A, 6 mo. later
6	6	++	0	0	Section	2A, 6 yr. later
7	7	++	0	0	Section	2A on discharge
8	8	+	0	+	Spontaneous	2A, 4 mo. later
9	8	+	0	0	Spontaneous	AF and failure 2 yr. later; died 5 yr. later
10	PP	+	0	0	Spontaneous	Bronchitis; 2A, 2 mo. later
Group II						
11	10	+++	0	0	Spontaneous	2A, 1 mo. later
12	10	++++	0	0	Spontaneous	2A, 8 mo. later
13	10	++++	0	+	Spontaneous	4 subsequent attacks of cardiac failure; death 5th attack 2 yr. later
14	PP	++++	0	0	Section	2A, 15 mo. later; alive 6 yr. later
Group III						
15	4	++	0	+	Spontaneous	Mild failure 2 mo. PP
	10	++	0	+		
	1 PP	+++	+	+		
16	5	++++	+	++	No	Died undelivered 2 hr. after admission
17	5	+++	+	0	No	Died undelivered 8th mo.
	8	++++	0	++		
18	5	+++	0	+	Section	Died 1 day PP
	PP	++++	0	0		
19	6	+++	0	0	Section	2A, 14 mo. later
	7	++++	0	0		
20	6	+++	0	+	Section	2A, 8 mo. later
	8	+++	0	0		
21	7	+++	0	0	Spontaneous	2A, 2 mo. later
22	8	+++	0	0	Section	2A at discharge
23	9	+++	0	0	Section	2A, 2 mo. later
Group IV						
24	4	+	+++	+++	Section at 5 mo.	Died 11 days PO
25	6	+++	++	+++	Section	2B, 1 yr. later
26	6	++	+++	+	Section	Mild failure 2 yr. later; 2A, 4 yr. later

\*PP, post partum.

PO, postoperative.

*Group I.*—There were 10 patients who had mild failure with a few persistent râles at the lung bases but little or no liver enlargement or edema. These signs appeared in different patients in almost every month of pregnancy and in the early puerperium, and all patients responded well to treatment.

*Group II.*—Four patients remained compensated throughout pregnancy but developed a marked degree of failure with delivery.

*Group III.*—There were 9 patients who developed a severe degree of heart failure before delivery, with signs of congestion principally in the lungs. Except for one who died in pulmonary edema two hours after admission to the hospital, all of them improved under treatment. Three of them (Cases 21, 22, 23) remained compensated during the remainder of the period observed. There were 5 in whom heart failure reappeared.

*Group IV.*—There were only 3 of the 26 patients in whom massive edema and marked liver enlargement developed in addition to the pulmonary congestion. All of them regained compensation and two were allowed to go to term.

#### NATURE OF THE HEART DISEASE

The cardiac findings in these patients have been analyzed in detail, so that they could be compared with the manifestations of heart failure by which these cases were grouped. The findings are recorded in Table II.

The type of valve lesion, previous history, and other cardiac findings listed in this table indicate a moderate degree of cardiac damage and are approximately the same for the patients who were classified as Groups I, II, and III on the basis of the nature of their heart failure. The patients in Group IV, on the contrary, all had advanced heart disease with large hearts and auricular fibrillation.

The factors which had an important bearing on the precipitation of heart failure in these pregnant cardiac patients as listed in Table II were many and need further explanation. Four patients were markedly overweight. In 6, coryza, sore throat, or hoarseness indicated that a respiratory infection immediately preceded the development of congestion of the lungs. Four patients had a slight degree of anemia, and three a severe anemia. One of these (Patient 20), who was admitted in heart failure during the fifth month of pregnancy, had a hemoglobin of 39 per cent, and a red blood cell count of 2 million. With liver and iron therapy and four small (125 to 150 c.c.) transfusions, her blood was restored to normal level before term. Another (Patient 17) was admitted in her second attack of heart failure during the eighth month of her pregnancy. She was in pulmonary edema, and a phlebotomy of 500 c.c. was necessary for relief. The following day her red blood cells numbered 2,900,000 and her hemoglobin 46 per cent. Six days later, when she had regained compensation, she was given a 100 c.c. transfusion. When a second transfusion was just beginning on the following day she developed a fatal attack of pulmonary edema.

In six patients there was some evidence of active rheumatism. The electrocardiograms of two showed questionable first degree heart block (PR 0.21). A third developed an acutely inflamed joint during her convalescence from heart failure. Another recovered from a typical attack of rheumatic fever just before pregnancy and two had pains without joint deformity during pregnancy. But these manifestations were not sufficient to indicate that an active rheumatic carditis precipitated heart failure in any instance.

Five patients had cardiac arrhythmias associated with heart failure. Two had probably been fibrillating for a long time. Patient 24 had been observed in the medical cardiac clinic for several years and her attack of heart failure followed the onset of auricular fibrillation. Patient 20 developed auricular fibrillation after recovery from decompensation, but her heart failure was not increased by it. The rhythm was reverted to normal by quinidine administration and continued so during the remainder of the observation. Patient 19 had three attacks of paroxysmal auricular tachycardia shortly after she was admitted in failure. There was no history to indicate that the failure was precipitated by such an attack and the passive congestion was not increased by the paroxysms observed.

TABLE II. NATURE OF THE HEART DISEASE AND COMPLICATIONS

CASE	VALVE LESION	PREVIOUS HEART FAILURE	PREVIOUS CARDIAC SYMPTOMS	RHYTHM	ELECTRO- CARDIOGRAM	CARDIAC ENLARGEMENT	REMARKS
<i>Group I</i>							
1	M. S.	Yes	Yes	Normal	RAD	None	
2	M. S.	No	No	Normal	RAD	Moderate	
3	M. S.	No	Yes	Normal	Normal	Moderate	Rheumatic fever immedi- ately before preg- nancy
4	M. S.	No	No	Normal	Normal	Slight	
5	M. S., A. I.	No	Yes	Normal	None	Moderate	URI; joint pains with- out deformity
6	M. S.	Yes	No	Normal	Normal	Slight	Obese
7	M. S.	No	No	Normal	PR 0.21	Moderate	Hg 65%
8	M. S., A. I.	No	No	Normal	Normal	Slight	R.B.C. 3.2 mil.; Hg 60%
9	M. S., A. I.	No	Yes	Normal	RAD; P <sub>1,2,3</sub> split	Marked	Hg 60%
10	M. S.	No	Yes	Normal	Normal	Slight	
<i>Group II</i>							
11	M. S.	No	No	Normal	None	No x-ray	URI; obese; R.B.C. 4.25 mil.; Hg 60%
12	M. S., A. I.	No	No	Normal	Normal	Marked	
13	M. S.	Yes	Yes	Normal	RAD	Slight	R.B.C. 3.8 mil.; Hg 40%
14	M. S.	No	No	Normal	Normal	None	URI
<i>Group III</i>							
15	M. S.	Yes	Yes	Normal	RAD	Moderate	Obese
16	Not de- termined	No	No	Normal	None	No x-ray	
17	M. S., A. I., A. S.	No	No	Normal	Normal	None	URI; R.B.C. 2.9 mil.; Hg 46%
18	M. S.	No	Yes	Normal	Normal	Moderate	
19	M. S.	Yes	Yes	Normal	RAD; PR 0.21	None	Paroxysmal auricular tachycardia
20	M. S.	No	No	Normal	Normal	None	Transitory auricular fibrillation; R.B.C. 2 mil.; Hg 39%
21	M. S.	No	Yes	Normal	RAD	Slight	URI; inflamed joint dur- ing convalescence from heart failure
22	M. S.	No	Yes	Normal	Normal	None	Obese
23	M. S.	Yes	No	Normal	Normal	Moderate	URI; joint pains with- out deformity
<i>Group IV</i>							
24	M. S.	No	Yes	Aur. Fib.	RAD; IVHB	Marked	Relative tricuspid in- sufficiency
25	M. S., A. I.	Yes	Yes	Aur. Fib.	LAD	Marked	
26	M. S.	Yes	Yes	Aur. Fib.	LAD	Marked	

The valve lesions are shown in the first column. M. S. refers to mitral stenosis, A. I. to aortic insufficiency, and A. S. to aortic stenosis. History of previous heart failure and of symptoms indicating an impaired cardiac reserve just before pregnancy are listed in columns three and four. The heart rhythm is shown in column five, the electrocardiographic findings in column six. RAD and LAD refer to right and left axis deviation, and when the conduction was delayed, the PR time is recorded. IVHB indicates an intraventricular heart block. The heart size by x-ray is shown in column seven. Extracardiac conditions which had a bearing on the development of heart failure are listed in column eight. URI indicates an upper respiratory tract infection, and in anemic patients the red blood cell count and hemoglobin are recorded.

## DISCUSSION

When a woman with heart disease becomes pregnant, a number of important problems relative to her management arise. The first of these is to determine whether the cardiac status will permit her to proceed safely with the pregnancy. This decision as well as the management of the patient throughout the remainder of her pregnancy will naturally depend upon an understanding of the patient's probable course. It is important to know how likely heart failure is to appear, what factors are responsible for its development, how it will first be manifest, and what course it will probably take. These questions are best answered by studying those patients who developed heart failure during pregnancy.

Only a small number of patients develop heart failure during pregnancy.

In our series, it occurred only 26 times in 620 pregnancies of patients with organic heart disease, an incidence of 4 per cent. This figure is considerably lower than any previously reported. Jensen,<sup>3</sup> from a review of the work of Carr and Hamilton,<sup>4</sup> Jasehke,<sup>5</sup> Fromme,<sup>6</sup> and Laennec,<sup>7</sup> concluded that about 20 per cent of women with heart disease develop failure during pregnancy. Bramwell and Longson<sup>8</sup> had 36 instances of failure among 350 patients with heart disease. The much lower incidence which we have found depends upon two facts. First, we selected only those patients showing physical signs of passive congestion. Although there were as many other patients who, because of the severity of their symptoms, were hospitalized early, given digitalis, or delivered by cesarean section, these were the only ones who showed definite objective evidence of heart failure. Second, the 620 patients were followed as closely as possible throughout their pregnancies in a special cardiac clinic and there can be no doubt that heart failure was prevented many times by careful management.

## CAUSE OF HEART FAILURE

Granted then that heart failure will develop in only a very small percentage of cases, the question arises: Why do these few patients develop it? A survey of the data in Table II indicates two causes. They are the degree of heart disease and the presence of those extra-cardiac factors which favor the development of heart failure in patients whose heart disease alone might not necessarily have caused trouble. This latter factor explains the appearance of heart failure in patients with only mildly damaged hearts and the lack of parallel observed above between the severity of heart disease and the degree of heart failure.

Only about half of our patients had sufficient evidence of cardiac damage to lead us to expect that their hearts might fail during pregnancy. There are reports of heart failures occurring in women whose hearts were perfectly normal before pregnancy but all the more reliable recent work indicates that heart failure develops only in those with well-recognized organic heart disease. With few exceptions they have mitral stenosis of the type seen after rheumatic fever, and the involvement of other valves is not usually important. Our cases were all of this type. The number of previous pregnancies appears to have no bearing on the development of heart failure but the factor of age

is as important in pregnancy as at any time. Of 1,633 patients with rheumatic heart disease studied by DeGraff and Lingg,<sup>9</sup> the average age for the development of cardiac insufficiency was 28 years, for the development of heart failure, 30 years, and the average age at death was 33 years. Our figures show the same approximate age grouping, since 16 of our 26 patients who developed heart failure were 30 or more years old. As Hamilton<sup>10</sup> has previously emphasized, age is one of the most important guides to prognosis of heart disease in pregnancy.

The functional classification of the American Heart Association which Pardee<sup>11</sup> first applied to the management of heart disease in pregnancy has been invaluable in the management of our cases. When the symptoms described by the patients did not appear compatible with the findings, exercise tests, especially stair climbing, were used. Among the patients who developed heart failure during pregnancy, 8 had previously had heart failure, and there were 14 who had symptoms in the months just prior to pregnancy, that indicated a diminished cardiac reserve. A large percentage of our patients showed enlargement of the heart by x-ray and even in those in whom the heart was of normal size, its configuration was distinctly abnormal. The electrocardiogram showed a right axis deviation in 8 of the cases, and 3 patients had auricular fibrillation.

A consideration of the data listed in Table II shows that the evidence of cardiac damage just discussed was not marked in about half of the patients who developed heart failure. In these cases there was usually an important extracardiac factor to account for it. In his book, *Failure of the Circulation*, Harrison<sup>12</sup> has listed the following as precipitating causes of heart failure: infection, exertion, cough, pregnancy, anemia, tachycardia, obesity, change of rhythm, emotional upsets, and prolonged mental strain. Almost all of these were found to be associated with heart failure in our series in addition to the pregnancy. Some of them seem to be considerably more important than others. Anemia was frequent and in two instances added considerably to the gravity of the situation. The factor of overexertion, which Hamilton<sup>10</sup> considers an important precipitating cause of heart failure during pregnancy, was not conclusively found to be such in any of our cases. It was, however, an important cause of the recurrence of heart failure. Upper respiratory tract infections were the most frequent and serious complications. Just how they affected the heart is not clear, for there was no definite evidence of any myocardial change in the patients with colds and bronchitis. This was also true of the patients who had rheumatic phenomena, for none of these showed sufficient electrocardiographic abnormality to indicate an active rheumatic myocarditis. One can only conclude that if rheumatic and respiratory tract infections cause myocardial change in pregnant women with heart disease, our present methods are inadequate to detect them. There seems to be little doubt, however, that in pregnant women, with relatively little evidence of cardiac damage, these infections have an important role in the development of congestive heart failure.

## MANIFESTATIONS OF HEART FAILURE

In 1933 Carr and Hamilton<sup>4</sup> reported that the incidence of heart failure increased progressively from the third to the ninth lunar month of pregnancy, after which it decreased progressively. Within the last year Cohen and Thomson,<sup>13</sup> working in Hamilton's department, have shown that those circulatory factors associated with the increased cardiac burden of pregnancy follow a curve which parallels that formed by figures of Carr and Hamilton. Contrary to these reports, Jensen,<sup>3</sup> who analyzed a much larger series of cases, was unable to find any particular time in pregnancy when heart failure was most likely to appear. The number of patients in our series is obviously too small to support or refute either of these findings. Our cases do show clearly, however, that there is no time after the second month of pregnancy when heart failure does not occur. Since the factor of cardiac work is not alone responsible for the development of heart failure during pregnancy, this is to be expected. In patients who have had heart failure before term and in those who have not, acute and severe decompensation is not uncommon within the first twenty-four hours after delivery or cesarean section. This fact, which has been well known for some time, has never been satisfactorily explained.

The data in Table I indicate that congestion of the lungs is by far the most frequent and important sign of heart failure during pregnancy. Even though peripheral edema is frequently seen in normal pregnancy, it was seldom present in the patients with heart failure and became marked only in those with auricular fibrillation. The latter likewise were the only ones to develop any significant degree of hepatic engorgement. This predominance of congestion of the lungs probably means that heart failure occurs in a more fulminating form during pregnancy than at other times. Moreover it is precipitated by the pregnancy before it would otherwise occur in the normal course of rheumatic heart disease. Congestion of the lungs is an early manifestation of heart failure, while edema and liver enlargement occur late. Pulmonary congestion was associated with paroxysmal nocturnal dyspnea in two patients (Patients 2 and 22) and with hemoptysis in five (Patients 2, 5, 19, 20, 21). It frequently became marked without other manifestations of passive congestion and progressed to acute pulmonary edema in seven patients. Acute pulmonary edema was the immediate cause of death in three of the four fatal cases.

## COURSE OF HEART FAILURE

The patients we have studied have taken several courses. Only four of them died. Those who showed mild manifestations of failure passed through the remainder of pregnancy without complications. There were four patients, however, who developed severe heart failure at term, even though they had had no signs of failure during pregnancy. Five of the nine patients who had relatively severe pulmonary congestion in early pregnancy developed a recurrence of it. Most of these relapses probably would not have occurred if the patient's activity

had been restricted more. Four of the 5 patients in whom a recurrence of heart failure developed had been allowed out of bed, and three of them had been allowed to leave the hospital. Moreover, two patients who had auricular fibrillation and advanced heart disease remained compensated in bed and were delivered by cesarean section.

Because of these experiences, we are convinced that patients who have once had congestive heart failure can almost always be maintained in a state of good compensation for several months even though the burden on the heart increases progressively as the pregnancy advances. There is good reason to believe that the work of the heart is decreased during the last few weeks of pregnancy. For these reasons, the interruption of pregnancy before term for congestive heart failure is indicated only in rare instances.

#### SUMMARY AND CONCLUSIONS

Among 22,837 patients with full-term and premature deliveries observed during the last six and a half years in the Woman's Clinic of the New York Hospital, 620 cases were complicated by organic heart disease. A study of those patients in this group who developed heart failure yielded the following information:

1. Congestive heart failure occurred in 4 per cent of the pregnancies complicated by organic heart disease. The mortality of those who developed congestive heart failure was 15 per cent.

2. The development of heart failure depended upon two factors: (a) severity of cardiac damage, and (b) extracardiac causes responsible for the precipitation of heart failure in women with slightly or moderately damaged hearts. These extracardiac causes were associated with the heart failure in approximately half of the cases. They included nearly all of the recognized precipitating causes of heart failure, but upper respiratory tract infections and anemia were the most important.

3. Congestion of the lungs usually was the only manifestation of heart failure in these patients. It was associated with hemoptysis in 20 per cent of them and progressed to acute pulmonary edema in 25 per cent. Acute pulmonary edema was the cause of death in 3 of the 4 fatal cases. Massive peripheral edema and marked liver enlargement occurred only in those with auricular fibrillation.

4. Heart failure developed during each of the last eight months of pregnancy and was not uncommonly first seen within the first twenty-four hours after delivery. It responded well to treatment but reappeared in about one-fourth of the patients. These relapses occurred only when the initial attack of failure was severe and would probably have been avoided in most cases if the patients had been more restricted in their activity.

5. With proper management almost all patients who have heart failure will improve and can be maintained in good compensation for several months, even though the burden on the heart increases pro-



gressively as the pregnancy advances. After the fourth month, the interruption of pregnancy for congestive heart failure is seldom indicated.

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525 EAST SIXTY-EIGHTH STREET

## THE MANAGEMENT OF PLACENTA PREVIA

### WITH AN ANALYSIS OF 260 CONSECUTIVE CASES\*

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**I**N THE ten-year period ending Jan. 1, 1939, 260 cases of placenta previa occurred in the 34,879 obstetric admissions to Charity Hospital of Louisiana at New Orleans, an incidence of 1:134. The maternal mortality in this series was 20, 7.6 per cent, and the gross fetal mortality 84, 32.3 per cent. Since the maternal deaths from placenta previa accounted for 8.3 per cent of the entire maternal mortality in the hospital during the period surveyed, it is obvious that this obstetric complication is worthy of thoughtful attention. An analysis of the series also reveals *interesting changes in obstetric practice during the years of the study, and a notable improvement in both maternal and fetal mortality as certain principles and procedures were put into effect.*

The cause of placenta previa is obscure, and in most respects this series throws no light upon it. In one regard, however, the figures are suggestive. In the obstetric admissions for the period surveyed, the proportion of multiparous to primiparous women was 1.7:1, whereas in the placenta previa cases it was 3.4:1. Some authorities have recently pointed out that parity does not predispose to placenta previa, but these proportions would seem to suggest that high parity may be of some etiologic significance. Frequency of gestation, furthermore, may play some part in the production of placenta previa, as may the occurrence of placenta previa in previous pregnancies. Seventy-one of the 202 multiparas in this series, 35.1 per cent, had had four or

\*Read at a meeting of the New Orleans Gynecological and Obstetrical Society, December 16, 1938.

more pregnancies in rapid succession, and 9 had had placenta previa in previous pregnancies. One patient had had 3 placenta previas in four years.

No racial difference was noted in the incidence of placenta previa. One hundred five of the 260 patients were white and 155 colored, which is approximately the proportion one would expect in view of the disparity between white and negro obstetric admissions.

#### ROUTINE OF MANAGEMENT

The key to the successful management of placenta previa, all authorities agree, lies in the employment of a routine which is practical at all times and which is applicable to any emergency. Since such a routine has been put into effect on the obstetric services of Charity Hospital for all cases of vaginal bleeding late in pregnancy, the maternal mortality from placenta previa in that institution has decreased some 36 per cent. This improvement, which has been chiefly noted in the last two years, is to be compared with the decrease in the mortality from placenta previa in the United States over the same period, which, according to the Children's Bureau, has been only 5 per cent.

The routine employed includes prenatal instruction of the patient; prompt hospitalization at the first sign of bleeding; establishment of the diagnosis by vaginal examination under strict aseptic precautions, after all preparations have been made for immediate delivery; preparation for blood transfusion and its employment as indicated; and termination of the pregnancy by an appropriate method as soon as the diagnosis has been confirmed.

*Prenatal Instruction.*—When the patient informs the physician that she has experienced genital bleeding, the first requisite in the proper management of placenta previa has been accomplished. Patients of the type with whom we deal in Charity Hospital, however, are very likely to ignore slight bleeding, and to pay no attention to the amount of blood lost, unless they have been specifically instructed on these points. Such carelessness is particularly typical of negro women in any condition in which pain is not a prominent symptom. The proper instruction of our patients is, therefore, an important part of our management of placenta previa. We tell them plainly that any genital bleeding is potentially very serious, even though it is a mere spotting, and insist that it be reported immediately. Tragic experiences have convinced us, like other obstetricians, that the risks inherent in the initial bleeding, however slight it may be, are grave enough to warrant a presumptive diagnosis of placenta previa, which immediate steps should be taken to establish or confirm.

*Hospitalization.*—Placenta previa is an obstetric complication for which home management is not safe. Because serious hemorrhage may recur at any time, and because even a careful vaginal examination may produce furious bleeding, it is essential that the facilities, equipment, and personnel of a hospital should be at one's immediate command. We therefore make no examinations in the home, and refer all our patients to the hospital as soon as any bleeding occurs. We also advise patients who live out of the city to make the trip to the hospital. Many individuals in this series were safely transported for distances of 50 or 100 miles by train or automobile, and serious bleeding did not occur in a single case in which the condition had been suspected by the local physician and no examination or manipulation had been attempted in the home.

The trouble and expense of hospitalization are warranted by the serious possibilities inherent in vaginal bleeding late in pregnancy. Some 70 per cent of all the patients referred to Charity Hospital for hemorrhage after the sixth month in the period covered by this study were found to have placenta previa or the equally serious complication of *abruptio placentae*.

*Diagnosis.*—In our experience, 50 per cent of all cases of painless genital bleeding in the last trimester of pregnancy prove to be due to placenta previa. In this series the initial hemorrhage occurred prior to the twenty-eighth week of gestation

in 7 cases, 2.6 per cent; between the twenty-eighth and thirty-seventh weeks in 81 cases, 31.1 per cent; and after the thirty-seventh week in 172 cases, 66.3 per cent. In most instances the bleeding was painless, but in 44 cases, 16.8 per cent, it was associated with the onset of labor, or occurred after labor had begun, and in a few other instances it was possible to trace it to trauma following intercourse or douching, or to some accidental fall or injury.

The actual diagnosis of placenta previa can be made only when the spongy, cushiony mass of the low-lying placenta is palpated on digital examination. Yet in spite of the importance of immediate diagnosis and the fact that the cause of the bleeding can be definitely established only by vaginal examination, we do not undertake such an examination until the following preparations have been made:

1. Donors are available for transfusion and remain available until we ourselves dismiss them.
2. Every provision is made for the control of bleeding and for the immediate termination of pregnancy by the vaginal or abdominal route as indicated.
3. The patient is surgically prepared and every provision is made for the accomplishment of a gentle vaginal examination under a strictly aseptic technique.

Only vaginal examination, in our opinion, supplies adequate information in this condition. If digital examination is not conclusive and placental tissue cannot be palpated, it is our practice to insert a bivalve speculum to aid in the differential diagnosis of other causes of painless bleeding, such as erosions, varicosities, polyps, and malignancy. We have found rectal examination of little value, and several cases in this series, in which profuse hemorrhage occurred after it had been done, show that it causes even more trauma than vaginal examination. Also we never use enemas. The roentgenologic diagnosis of placenta previa by means of sodium iodide or air introduced into the bladder has not furnished conclusive evidence in our hands, and we are unwilling to rely upon it for accurate information. We consider amniography dangerous and never employ it.

Complete placenta previa, in which the entire os of the cervix is covered by the placenta, was present in 96 of our 260 cases, 37 per cent. Partial placenta previa, in which the placenta covers only a portion of the os, was present in 86 cases, 33 per cent. In practice, we state the exact portion of the os covered by the placenta in terms of 25, 50, and 75 per cent. Marginal placenta previa, in which the placenta borders on or touches the cervical os, was present in 78 cases, 30 per cent. In this study low implantation, in which the placenta is attached to the lower uterine segment but the edge is above the internal os, has been classified with marginal implantation. It is the least severe type, and is frequently overlooked if the bleeding is slight or if labor progresses rapidly.

#### TRANSFUSION

It is our practice to procure donors as soon as the patient enters the hospital and before internal examination or any other procedure is attempted, and to keep them available until it is quite certain that their services will not be immediately required. If there has been a serious loss of blood, a transfusion is given before diagnostic or therapeutic measures are instituted. If the blood loss has not been great, the sterile vaginal examination is proceeded with and transfusion is done if hemorrhage ensues or as the need becomes evident during treatment. In most instances the measure is deferred until after delivery, when it is now our practice to employ it routinely. The patient may require one transfusion or several, depending upon the estimate of the amount of blood lost. In the average case we usually give 650 c.c. of blood.

A study of the Charity Hospital figures furnishes conclusive proof of the value of transfusion in placenta previa. Only 34 per cent of the 260 patients who com-

prise the series were transfused. On the other hand, 88 per cent of the patients with placenta previa seen during the last two years were transfused, as was every patient seen during the last year, and the notable improvement in mortality closely parallels the increasing use of blood. In many of these cases, in our opinion, puerperal infection was prevented by the early correction of anemia.

The administration of blood is the only method of permanently correcting blood loss, but if blood should not be immediately available, the depleted body fluids may be temporarily restored by the use of glucose solution (500 c.c. in 10 per cent concentration) or acacia solution (500 c.c. in 6 per cent concentration) introduced by vein, or by the introduction of 1,000 c.c. of Ringer's solution by hypodermoclysis. The parenteral administration of fluids usually improves the clinical picture, but such patients should always be carefully observed until blood is available, for a false sense of security may be created and shock may occur several hours after the good effects have worn off.

#### METHODS OF DELIVERY

There is no expectant treatment of placenta previa. As soon as the diagnosis is confirmed by vaginal examination, the appropriate method for terminating pregnancy should be instituted, without regard for the viability of the child. As a matter of fact, the fetal prognosis is not improved by a waiting policy, and the maternal prognosis is made very much worse. Nine of the 20 maternal deaths in this series occurred in patients who had been bleeding for more than 5 days, and in no instance was a live child secured.

We endeavor to individualize our patients, and have no set plan for accomplishing delivery in these cases. Certain general principles, however, determine our course. The selection of the method of intervention is dependent upon such considerations as the type of placenta previa, the condition and parity of the patient, the stage of pregnancy, and the status of the fetus. The experience and ability of the obstetrician, and the facilities and amount and kind of equipment available, unfortunately cannot always be ignored. If by ill chance the patient is not in a hospital and cannot be admitted to one, we believe that major obstetric procedures should never be attempted.

Whatever form of therapy is adopted is directed toward: (1) the control of hemorrhage; (2) the replacement of blood loss; (3) the selection of the most rapid method, compatible with safety, of terminating the pregnancy; (4) avoidance of trauma; and (5) prevention of infection.

#### DELIVERY FROM BELOW

One hundred and sixty-two patients, 62.3 per cent, were delivered by the vaginal route, with a maternal mortality of 11.1 per cent and a gross fetal mortality of 45.7 per cent. The following methods were employed:

Rupture of the membranes in 80 cases (60 marginal, 20 partial) with a maternal mortality of 5 per cent and a fetal mortality of 27.5 per cent.

Willetts' method of scalp traction in 6 cases (4 partial, 2 marginal) with 0 maternal mortality and a fetal mortality of 16.6 per cent.

Breech traction in 5 cases (3 partial, 2 marginal), with 0 maternal mortality and a fetal mortality of 20 per cent.

Mctureury's in 40 cases (11 complete, 19 partial, 2 marginal) with a maternal mortality of 12 per cent and a fetal mortality of 62.5 per cent.

Braxton Hicks' version in 21 cases (8 complete, 10 partial, 3 marginal) with a maternal mortality of 24 per cent and a fetal mortality of 80.9 per cent.

Vaginal tamponade in 10 cases (4 complete, 5 partial, 1 marginal) with a maternal mortality of 40 per cent and a fetal mortality of 80 per cent.

Even a casual survey of these figures makes it clear that the first three methods are far safer for both mother and child than the last three. On the other hand, although rupture of the membranes, Willett's scalp traction, and breech traction are simple and safe methods in themselves, part of their apparent good results in this series must be attributed to the fact that they were used in the management of the

simpler cases of placenta previa. There is no doubt, however, that metreurysis, Braxton Hicks' version, and vaginal tamponade are actually or potentially dangerous, and it is not surprising to find in the later years of this study that many cases in which they would once have been employed were managed by cesarean section.

Rupture of the membranes is a simple and effective method in the less serious cases of incomplete placenta previa, though in our opinion it is rarely suitable for the management of the complete type. It is also the first step in any mode of intervention which aims at delivery through natural channels. The release of the amniotic fluid permits the presenting part to descend into the pelvis, and bleeding is thus controlled by a sort of natural tamponade. We have found that the degree of compression can be materially increased by the application of a tight abdominal binder. If the patient is not having pains, we endeavor to precipitate labor by the administration of pituitary extract (1 minim doses at twenty-minute intervals).

Willett's method of scalp traction was devised for cases in which the child is dead or nonviable, but we have used it several times recently on living children, with excellent results. If bleeding continues after rupture of the membranes, in primary breech presentations, a foot may be brought down and slight traction exerted to compress the placenta by the buttocks against the uterine wall.

Braxton Hicks' version, which should not be confused with the simple and safe method of breech traction just described, is still useful in emergencies, when the child is dead or previable, or when other methods for the control of hemorrhage cannot be employed. It is, however, a difficult and dangerous maneuver, and we do not recommend it. A vaginal pack is not an effective method for the control of hemorrhage, and its introduction, like the introduction of a bag into the uterus, predisposes to infection. If metreurysis should be employed, we prefer intraovular insertion of the bag, because it permits its close application against the placenta, and we always use the largest size (11 cm.), so that the cervix will be sufficiently dilated after the bag has been extruded to permit immediate delivery of the child, by forceps or by version and slow extraction if spontaneous delivery does not seem imminent. We also prefer manual traction to traction by weights, because unregulated force is likely to result in tears of the friable tissues of the lower uterine segment.

#### MANAGEMENT OF THE THIRD STAGE OF LABOR

Active treatment was required after delivery in 44, 27 per cent, of the 162 patients in this series who were delivered by the vaginal route. Four required more than one procedure to control the hemorrhage. Manual removal of the placenta was done in 12 cases, repair of lacerations in 17, and packing of the uterus in 19.

These figures are significant, for it is often not realized that complications of the third stage of labor and of the post-partum period may contribute materially to the mortality of placenta previa. Hemorrhage may follow the birth of the baby or the expulsion of the placenta, but may not occur until several hours or even several days after delivery. It may originate from the placental site or from lacerations of the birth canal. It is not always possible to prevent post-partal hemorrhage in placenta previa, but if the possibility is realized and the bleeding recognized as soon as it occurs, and managed properly, it is rarely of serious consequence.

#### DELIVERY BY ABDOMINAL SECTION

The data from Charity Hospital are in accord with reports in the literature as to the increasing use and real value of cesarean section in the management of placenta previa. It was used in 27 per cent of the cases in the first five years of this survey, and in 45 per cent in the second five years. During the second period 91 per cent of all cases of complete placenta previa were managed by the abdominal route, against 55 per cent in the first period. The relative mortalities of 5.1 per cent for the last five years and 11.3 per cent for the first period testify to the wisdom of the increasing use of this method.

The figures from Charity Hospital also illustrate the increasing use of laparotomies. This operation was used in only 31 per cent of the cases of placenta previa managed by abdominal section prior to 1934, but in 52 per cent of the cases

seen since then, and in the last year, it was used routinely in deliveries by the abdominal route. Laparotrachelotomy has several distinct advantages over the classical type. It furnishes rapid, direct access to the field of bleeding. It is associated with less risk than the classical section in potentially infected cases. There is less likelihood of rupture of the uterus in subsequent pregnancies, because the scar is in the noncontractile portion. Our experience has shown that post-partal hemorrhage is not likely to occur after cesarean section if a tight gauze pack is inserted into the uterus through the uterine incision and kept in place for eight hours.

In patients who are obviously infected from unsterile examination or improper maneuvers, the Porro operation has a distinct field of usefulness. It was employed in 9 patients in this series, in 3 of whom the presence of fibroids furnished an additional indication for hysterectomy.

#### MATERNAL AND FETAL MORTALITY

The mortality reported for placenta previa varies according to circumstances. In the practice of an experienced obstetrician it is likely to be low among patients whose pregnancies he has supervised throughout, and it is usually low in well-organized maternity clinics in which prenatal care is adequate. Neglected patients supply the major portion of both fetal and maternal mortality. In this connection, it is significant that at Charity Hospital the maternal mortality for the whole series of 260 cases was 7.6 per cent, but that, when the figure was broken down, the white mortality was found to be 5.7 per cent and the negro 9 per cent.

The condition of the patient is an extremely important factor in the mortality. In 3 of the fatal cases in this series, the patients were admitted in shock. One other patient was moribund on admission, and one was gravely ill with pneumonia, which had been present for two weeks. It is significant that the 3 patients admitted in shock, as well as the patient admitted moribund, had been examined at home, with no preparations to control the furious hemorrhage which resulted in each case. In 5 of the fatal cases the condition of the patients was fair on admission, and in 10 it was good, which introduces the immediate implication that the management of these cases, and not the placenta previa per se, was responsible for the fatal outcome.

The causes of death in the Charity Hospital series agree with those listed in practically every report in the literature. Nine patients died from hemorrhage, 6 from rupture of the lower uterine segment, 4 from infection, and 1 from pneumonia. Some of these deaths were clearly due to the traumatic manipulations used to control hemorrhage, which resulted in rupture of the uterus or the introduction of infection. It is significant, for instance, that of the 5 deaths following Braxton Hicks' version, 3 were due to rupture of the uterus and 2 to hemorrhage, and that in some of these cases immediate extraction had been attempted after the version, without regard to the degree of dilatation.

Another consideration in the maternal mortality in this series from Charity Hospital also deserves emphasis. The general maternal mortality in the 260 cases was 20, 7.6 per cent. But the rate in delivery from below was 11.1 per cent, more than five times higher than the rate in delivery by cesarean section, 2.0 per cent. Only 2 patients died after cesarean section, both from puerperal infection, one after high and one after low section. In the 73 cases of complete placenta previa terminated by section there was one death, 1.3 per cent, against 8 deaths, 35 per cent, in the 23 cases handled from below. These disproportions are all the more significant when it is recalled that the most serious cases were handled by cesarean section. On the other hand, these favorable figures should not lead to the use of abdominal section in all cases of placenta previa. The proper selection of cases will give better results than the routine and indiscriminate use of this method.

The gross fetal mortality was 32.3 per cent and the corrected fetal mortality 13.8 per cent. In many instances the babies were dead when the mothers were admitted, or were previable, and much of the fetal mortality was therefore unpreventable. A further correction might well be made for the large number of premature and immature infants who were delivered alive but did not survive.

Both the total (32.3 per cent) and the corrected (13.8 per cent) fetal mortality were less in the complete type of placenta previa (29.1 per cent, 10.4 per cent) than in the partial variety (38.3 per cent, 17.4 per cent). This disparity is explained by the fact that most cases of complete placenta previa were managed by cesarean section, in which the child's chances of life are enhanced.

At Charity Hospital the fetal mortality was 5.1 per cent in the cases managed by cesarean section, against 19.2 per cent, almost four times as much, in the patients delivered by the vaginal route. It is only fair to add, however, that in some of these cases the status of the fetus on admission seems to have been the factor in deciding upon vaginal rather than abdominal delivery.

#### SUMMARY AND CONCLUSIONS

1. A series of 260 consecutive cases of placenta previa is reported from Charity Hospital of Louisiana at New Orleans for the 10-year period ending Jan. 1, 1939. The maternal mortality was 7.6 per cent, the gross fetal mortality 32.3 per cent, and the corrected fetal mortality 13.8 per cent.

2. A definite routine is outlined for the management of bleeding in the last trimester of pregnancy, including: immediate hospitalization for diagnosis and treatment at the time of the first hemorrhage; confirmation of the diagnosis by vaginal examination under strict aseptic precautions, after every provision has been made for the control of hemorrhage and for any type of delivery; the immediate termination of gestation when the diagnosis of placenta previa has been established; preparation for transfusion before any vaginal examination or manipulation is attempted.

3. It is emphasized that no patient is likely to die from the first hemorrhage or from the delay necessary for the preparations outlined if internal examination or manipulation has not been attempted.

4. It is also emphasized that blood losses should be corrected by transfusion in every case of placenta previa, and that donors should be kept available until there is no longer any possible need for their services.

5. Rupture of the membranes, control of hemorrhage by Willett's scalp traction or by breech traction, metreurysis, Braxton Hicks' version, and vaginal tamponade were used in the 162 cases in this series in which delivery from below was employed. The last three methods, which give results far inferior to the first three, and which are potentially dangerous, are no longer very generally employed. There was noted an increasing tendency to employ cesarean section, particularly the low operation, in most cases of complete and many cases of partial placenta previa. It offers the best prognosis for the child, and in competent hands and properly selected cases is quite safe for the mother.

6. Deaths in placenta previa are chiefly due to hemorrhage, sepsis, and rupture of the lower uterine segment. These causes are largely preventable, and such deaths continue to occur, chiefly because patients delay seeking medical consultation and because many physicians are not fully aware of the potential seriousness of all hemorrhage in the third trimester of pregnancy and are unprepared to handle this complication.

## PLACENTA CIRCUMVALLATA

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ALTHOUGH during the past sixty years much investigation has been done in the study of placental pathology, many questions are still unanswered and much information is yet to be obtained before this transient, intermediary organ between mother and fetus, is clearly understood. The recent study of Streeter of the developing monkey ovum, offers a very valuable approach to the solution of many of these problems.

There are, however, many lesions of the placenta which may be clarified with the information available today. It is our desire to call attention to one particular variety of placental abnormality, viz., placenta circumvallata, and to attempt to elucidate some of the widespread confusion regarding its clinical significance.

We have as a basis for our exposition a study of the clinical histories and pathologic examinations of 150 cases of definite placenta circumvallata, observed in 20,720 deliveries. Only single pregnancies have been considered. All cases of marginal infarction, placenta marginata, and other forms simulating the gross appearance of placenta circumvallata have been carefully excluded.

In 1934, Hobbs and Rollins, noting the frequent association of this condition with certain clinical phenomena, reported their study of the first 79 cases of this present series.

Placenta circumvallata may be defined as an abnormal development of the placenta, characterized by a restricted growth of the chorionic plate, with oblique growth of its marginal villi into the surrounding decidua vera to form an extrachorial margin of placental tissue around part or all of its circumference. The membranes which insert into the edge of the plate become reduplicated and form a fold lying on the plate and constitute a wall of varying thickness around it.

If the fold is not present, the condition is commonly spoken of in the German literature as placenta marginata. The term placenta circumvallata is reserved for the type with the fold of membranes and is considered as only a further development of the secondary changes incident to the limit of growth of the chorionic plate.

The number of terms used in the literature to designate this condition is altogether too numerous and most confusing. Williams pointed out the need for simplification of the terminology. Some of the most common terms found in the literature will be mentioned so that there will be a clear understanding of the nomenclature.

In the American literature the term placenta circumvallata is most widely used. DeLee uses the term "neppiformis" synonymously with circumvallata, Goodall



uses placenta circumvallata in the usual sense and has added the term circumcrescent to designate the type without the fold of membranes which corresponds to the marginata of the German literature.

The most frequently used designations in the German literature, which is by far the largest on the subject, are placenta marginata and placenta circumvallata as given in the definition above. Robert Meyer, who has studied some 300 specimens, suggested using the term placenta extrachorialis. This term, although quite descriptive, has not been widely accepted. The French use the terms *marginé*, *Brodé* and *collarete*.

This confusion of names and their application is reflected in the wide discrepancy of the incidence of the abnormality, as reported by various authors. Williams found it occurring in 1 to 2 per cent of his cases, von Herff 7.6 per cent, Bertkau 14 per cent, and Del Vivo 21.3 per cent. We have found the incidence of placenta circumvallata to be 0.8 per cent in single pregnancies.

The theories of etiology and the method of formation of this anomaly have been described in detail by Williams and generally accepted.

A thorough understanding of the developmental anatomy is indispensable for the intelligent discussion of the clinical significance of this abnormality. To emphasize the importance of this aspect we will quote two leading authorities.

Williams, who studied some 30 cases of term and near term specimens, states, ". . . upon going over the clinical histories of patients presenting the abnormality, my impression is that it is practically without clinical significance." On the other hand Seitz in Stoeckel's *Lehrbuch der Geburtshilfe* for 1935, states, "Placenta marginata (German terminology for circumvallata) has certainly a definite clinical significance. One has ground to state that in pregnancy protracted bleeding and many abortions have their cause in this irregularity of the placenta. Also difficulty is more often encountered in the third period when complicated by placenta marginata." Hinselman, Sarway and Bumm, and other leading German authorities are of the same opinion, while in this country, Williams' opinion has been generally accepted and recorded in our leading textbooks and references. DeLee and Goodall have stated that this condition may cause clinical complications without giving any factual data. We have been unable to find a report of a clinical study of this abnormality.

It is very important to obtain accurate information concerning this abnormality. Is it an etiologic factor in abortion? Does it cause last trimester bleeding which might be confused with the bleeding from placenta previa? Is it responsible for some fetal deaths? Does it cause difficulty in separation of the placenta? Is it dangerous to the mother? How shall such cases be managed?

In this study of 150 cases, we believe that we have a large enough series to give some accurate information. Several factors must be considered in determining the outcome in cases of placenta circumvallata: (1) The period of pregnancy when the chorionic plate becomes restricted; (2) the degree of restriction; (3) the percentage of circumferential restriction; (4) the functional reserve of the placenta at the time this condition occurs; (5) subsequent reduction of the placental function by infarction, etc.; (6) the ability of the trophoblast

to create new placental spaces; and, (7) the irritability of the uterus. The outcome is dependent on the time, degree, and multiplicity of these factors.

In considering the clinical aspects of this anomaly, naturally one's attention is directed to: First, the effect on the fetus, and second, the effect on the mother.

To those who are familiar with the development of placenta circumvallata, it is obvious that the fetus may be affected in the following ways: First, restriction of the growth of the plate and the inability of the villi to create new placental spaces sufficient to meet all the increasing demands of the fetus, may lead to death. This placental deficiency may be augmented by placental infarction. If the fetus perishes early, abortion will occur. Later in pregnancy the placental reserve may be used up and the fetus may die just before term. Under ideal conditions the placental reserve may be sufficient to carry the fetus to term. This not infrequently happens and accounts for the report of Williams where only term or near term placentas were examined.

If one has examined the extrachorial margin of a circumvallate placenta, it will be recalled that the fetal surface is bounded not by the strong chorionic plate, but by the delicate decidua and overlying membranes. Motion of the uterus when this area is under tension in an attempt to keep pace with the expanding placental site may easily cause a rupture through the decidua into the intervillous spaces and thereby produce bleeding which may be concealed if the uterine cavity is obliterated or it may be revealed by dissecting the membranes from the decidua vera. Fortunately the blood pressure in the intervillous spaces is very low so that the bleeding is rarely, if ever, alarming. From this disturbance of the pregnancy, premature labor is often induced. If the child has reached the viable period, it is frequently born alive, provided there has been adequate placental function until this accidental hemorrhage initiated labor. Abortion, death of the fetus and premature labor are complications that may occur in cases of placenta circumvallata.

The usual effects on the mother are as follows: (1) Hemorrhage from incomplete abortion, although these abortions are usually complete, because they occur after the placenta has developed. (2) Blood loss from rupture of the marginal intervillous spaces as described above. It causes irregular, painless bleeding simulating placenta previa, especially if it occurs during the last trimester of pregnancy. (3) Occasional difficulty in the separation of the placenta because of the abnormal growth of the villi deeper into the decidua and occasionally into the uterine muscle.

#### SUMMARY

Table I is a composite picture of the 150 cases studied.

1. The duration of pregnancy is classified according to the number of weeks when known, as follows: under 27 weeks are abortions; 27

TABLE I.\* A COMPOSITE PICTURE OF A CLINICAL AND PATHOLOGIC STUDY OF 150 CASES OF PLACENTA CIRCUMVALLATA OCCURRING IN 20,720 CONSECUTIVE DELIVERIES, AN INCIDENCE OF 1 TO 138 OR 0.8 PER CENT

CLINICAL CLASSIFICATION	FETAL MORTALITY			TYPE OF CIRCUMVALLATION		AVERAGE DURATION OF PREGNANCY WEEKS	PARITY		PRE-LABOR BLEEDING CASES	RETAINED PLACENTA		WASSERMANN	
	STILL-BORN OR DIED IMMEDIATELY	SIZE FOR VIABILITY (117 CASES)	TOTAL	COMPLETE PER CENT	PARTIAL PER CENT		PRIMITIVE ARAS	MULTIPLE ARAS		PERIODS OF GESTATION	TOTAL	PERIODS OF GESTATION	TOTAL
Abortions 33 cases 22%	33 cases 100%			51	49	24	10 cases 33%	23 cases 67%	18	6 cases 18%		Negative, 19 cases Positive, 4 cases Unknown, 10 cases 17% of known have positive serology	
Prematures 23 cases 16%	9 cases 39%	16 deaths, 14%	49 babies, 33%	38	62	31	7 cases 33%	16 cases 67%	6	1 case 4%	12 cases 8%	Negative, 17 cases Positive, 3 cases Unknown, 3 cases 15% of known have positive serology	107 known cases 25% positive serology
Term 94 cases 62%	7 cases 7%			41	59	39	28 cases 30%	66 cases 70%	9	5 cases 5%		Negative, 44 cases Positive, 20 cases Unknown, 30 cases 31% of known have positive serology	

\*Abortion, fetus weighing under 1500 gm. and less than 25 cm. in length.

Prematures, fetus weighing between 1500 and 2500 gm., and between 25 and 45 cm. in length.

Term, fetus weighing over 2500 gm., and over 45 cm. in length.

to 38 weeks are premature; and, 38 to 42 weeks are term deliveries. This method is obviously quite inaccurate so the weight-length measurements were also used as defined beneath the table.

2. The incidence of abortion and premature labor is very high as compared to the average group of pregnant women. It must be kept in mind that this group of 150 women, other than the abnormality of the placenta, represents a typical sample of clinic and private practice.

3. A fetal mortality of 14 per cent in babies born after the twenty-seventh week emphasizes the seriousness of placenta circumvallata. A total mortality of 33 per cent places this abnormality as one of the outstanding feticides.

4. We have classified all of the specimens either as complete or partial circumvallata. On first consideration one would think that the complete type would be much more effective in producing complications during pregnancy. However, when one considers that the majority of the partial variety included 50 per cent or more of the circumference and many were almost complete, it can be understood why they are as effective as the complete variety in causing complications.

5. The average duration of pregnancy for the series is 32.5 weeks. Some German authors claim that postmaturity is frequently associated with this condition. We cannot substantiate this observation. Most labors occurred around the twentieth week.

6. For some unknown reason parity plays a role in the occurrence of placenta circumvallata. Multiparas outnumbered primiparas about two to one in each classification. A count of primiparas and multiparas in successive deliveries in the St. Louis Maternity Hospital for a year showed approximately equal numbers. The youngest patient in this series was 18 years old and the oldest was 42.

7. We wish to call attention especially to the uterine bleeding produced by this condition. Thirty-three cases showed prelabor bleeding. It was painless, intermittent in character; although it lasted several weeks at a time, it was usually mild. It occurred at any time during pregnancy and was not always followed by the onset of labor. Many patients bled intermittently for many weeks and delivered a live infant at term. In none of the patients was the bleeding serious, and with bed rest and sedation there was a tendency for cessation of bleeding. If the fetus perished, labor usually soon followed.

The most important clinical aspect of this condition is the awareness that painless bleeding during the last trimester is not always pathognomic of placenta previa. A few of these cases were brought into the hospital with that tentative diagnosis. Vaginal examination failed to confirm the diagnosis of placenta previa, and with bed rest the bleeding usually ceased. Unlike placenta previa, bleeding from a circumvallate placenta does not tend to be more severe with each recurrence. It is extremely important to be aware of this condition, for although there is little to be done for these patients, it is a serious mistake to treat them actively for the mistaken diagnosis of placenta previa.

8. Twelve patients had retained placentas. These cases were handled in the usual conservative manner. After a reasonable period of time, manual removal was necessary.

9. The incidence of syphilis (25 per cent of 107 known cases) was about twice the average in the clinic population. Many of these cases were under antisyphilitic treatment before the onset of pregnancy, and all syphilitic patients received treatment as soon as diagnosed, no matter what the stage of pregnancy. The etiologic relationship, if any, of syphilis to the formation of placenta circumvallata is not clear.

10. Hunt reported two cases of hydrorrhea gravidarum associated with placenta circumvallata. In our series four definite cases were noted. In a previous article by one of us, a picture of the placenta of such a case was recorded. We have a placenta, which is not included in this series, since it was delivered after the compilation of these statistics, from a woman who had an intermittent discharge of large amounts of fluid from the sixth month until term. It appears that hydrorrhea gravidarum is frequently associated with this condition.

#### CONCLUSIONS

From a study of this series of 150 cases of placenta circumvallata, we feel justified in making the following conclusions:

1. The occurrence of this abnormality is much less frequent than most writers have stated. As a result of confusion in terminology and lack of definite criteria for identification, many cases of marginal infarction, etc., have been reported as cases of circumvallation. The incidence of the anomaly in our series is 0.8 per cent.

2. It is of considerable clinical significance. It frequently terminates in an abortion (22 per cent). It often causes premature labor (16 per cent). The mortality is high (33 per cent). Painless bleeding, which occurred before the onset of labor, happened in 22 per cent of the cases. When the bleeding appeared during the last trimester of pregnancy it was mistaken for placenta previa in some instances.

3. In cases of hydrorrhea gravidarum this abnormality should be suspected.

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## A STUDY OF CERVICAL POLYPS

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THE universal proof that hyperplasia of the endometrium is of estrogenic origin served to intensify interest in the possible existence of an etiologic relationship between other pathologic conditions of the uterus and abnormal hormonal states.<sup>1</sup> To maintain, however, that the coexistence of either benign or malignant tumors of the uterus and endocrine disorders is more than mere coincidence, implies a greater certainty than the facts yet warrant. Clarification of this important problem may be attained, as indicated in several recent studies on myoma<sup>2</sup> and carcinoma<sup>3</sup> of the uterine body, through detailed analysis of all factors related to uterine tumors. In pursuance of this thought, the various clinical and pathologic aspects of cervical polyps are herein considered.

The present report comprises a group of 117 consecutive patients with cervical polyp observed at the Mount Sinai Hospital during the period between Jan. 1, 1933 and Dec. 31, 1937. Of the 117 patients, 21 were treated in the outpatient department and 96 were hospitalized.

### FREQUENCY

Reports on the incidence of cervical polyps as a gynecologic entity vary according to the source of the data. For instance, in an analysis of tissues removed during 1,000 consecutive gynecologic operations, Fetterman<sup>4</sup> found a 10 per cent incidence of cervical polyps. A study by Geiger,<sup>5</sup> on the other hand, of 2,048 gynecologic patients admitted to a tumor clinic revealed only 1.5 per cent of cervical polyps. Ninety-six of the 117 instances of cervical polyps herein reported were encountered in 3,900 hospitalized patients who underwent gynecologic operations, an incidence of 2.4 per cent.

The usually benign character of a cervical polyp, its ease of removal, and the permanence of such treatment make it a minor gynecologic lesion and relegate it to the limbo of "office gynecology." For this reason, its actual frequency cannot be ascertained from statistics based entirely on hospital experience. Elsewhere<sup>6</sup> it was noted that 23 women with cervical polyps were found among 163 patients with irregular uterine bleeding examined in office practice—an incidence of 14.1 per cent. This higher frequency of cervical polyps, when viewed from the standpoint of the leading symptom, augments their clinical importance.

### AGE INCIDENCE

While the occurrence of a cervical polyp is not limited to any age period, 41 per cent in the present series were found during the fifth decade (Fig. 1). This is in accord with the earlier reports of Schroeder,<sup>7</sup> Fluhmann,<sup>8</sup> and Geiger.<sup>5</sup> The climacteric, denoting the natural decline of ovarian function, does not protect the woman from the cervical polyp. Forty-five of these 117 women (39.3 per cent) came under observation after the menopause.

Childbearing has an apparent influence on the incidence of cervical polyps, inasmuch as 99 of the 117 patients (84.6 per cent) had borne one or more children (Table I).

TABLE 1. INFLUENCE OF PARITY ON THE INCIDENCE OF CERVICAL POLYPS IN 117 PATIENTS

PARITY	NUMBER OF PATIENTS	PERCENTAGE
Multiparous	90	77.0
Primiparous	9	7.6
Nulliparous	18	15.4

## SYMPTOMS

In the present series of 117 patients with cervical polyps, 60 (51.3 per cent) had abnormal uterine bleeding, 14 (12 per cent) complained of leucorrhea, and 43 (36.7 per cent) were free from symptoms attributable to polyps. In the latter group, the polyps were discovered during routine examination. This fact coupled with the frequency with which polyps complicate other gynecologic lesions makes it difficult to determine the precise significance of the cardinal symptoms of cervical polyps, namely, abnormal uterine bleeding and leucorrhea.

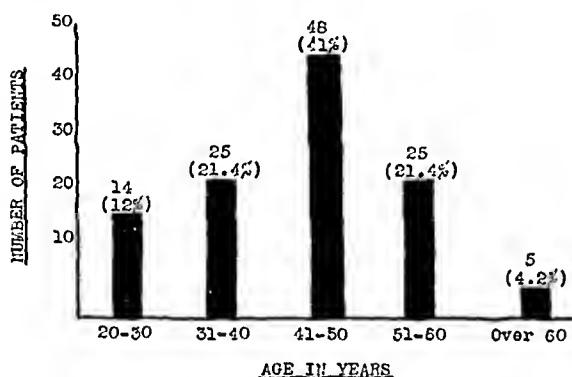


Fig. 1.—Age incidence of cervical polyps in 117 patients.

The abnormal bleeding, often the portentous signal of genital carcinoma, lends clinical dignity to the cervical polyp. Except in instances of vaginal bleeding following coitus or douching (contact bleeding), of which there were only 10 in this series, the source of the bleeding is not always clear. This is especially true when an associated pathologic condition such as uterine myoma is present. It is, moreover, possible that bleeding, in some instances, may arise from a hyperplastic endometrium and not from the polyp. The two conditions may, according to Geist,<sup>9</sup> have a single endocrine etiology—a theory which still seems to have more of shadow than of substance.

Either menorrhagia or metrorrhagia may occur, but the latter is more likely to be caused by the polyp alone. Of the 60 patients with abnormal uterine bleeding in the present group, 40 had metrorrhagia, 13 menorrhagia, and 7 had both. It is noteworthy that 16 of the 40 patients with metrorrhagia were beyond the menopause.

The low incidence (12 per cent) of pronounced leucorrhea as a leading symptom seems unusual, especially in view of the frequent coexistence of cervical polyps and chronic cervicitis (Table II). It emphasizes, perhaps, the tendency of women to look lightly upon the presence of leucorrhea.

## ASSOCIATED GYNECOLOGIC CONDITIONS AND ETIOLOGY

Cervical polyps are often dwarfed into insignificance by coexisting symptoms producing pelvic lesions (Table II).

Etiologically, the coexistence with cervical polyp of vaginal relaxation, uterine myoma, pregnancy, chronic pelvic inflammatory disease, and ovarian cystadenoma

TABLE II. INCIDENCE OF GYNECOLOGIC CONDITIONS ASSOCIATED WITH CERVICAL POLYPS IN 117 PATIENTS

ASSOCIATED GYNECOLOGIC CONDITION	*NUMBER OF PA-TIENTS	PERCENTAGE
None	34	29.0
Chronic cervicitis	73	62.4
Relaxation of vagina (cystocele, rectocele, and uterine descent)	20	17.0
Uterine myoma	10	8.5
Pregnancy	5	4.2
Chronic pelvic inflammation	4	3.4
Ovarian cystadenoma	1	0.8

\*Two or more associated pelvic conditions were present in 30 patients (25.6 per cent), thereby accounting for a total number more than 117 in this table.

is of little importance because the respective incidence of these conditions in this group of 117 polyp-bearing patients is comparable to that found in any similar group of women. The absence, however, of an accompanying pelvic condition in 29 per cent of the patients is significant and bespeaks an independent origin of cervical polyp. Nor is the latter conception invalidated by the apparently overshadowing incidence (62.4 per cent) of chronic cervicitis as a co-existing lesion. This is supported by the fact that 99 of this series (84.6 per cent) were parous women, a group in whom the incidence of cervicitis is customarily high. Nevertheless, the higher incidence of both cervical infection and polyps in parous women suggests that the cervical trauma of childbirth may be the common etiologic denominator of both conditions.

The belief that a cervical polyp is a neoplasm, the growth of which is perhaps influenced by trauma sustained through childbearing, does not necessarily preclude the possibility of a causative endocrine factor. For that reason, an attempt was made to analyze the possible relationship of cervical polyp to endometrial hyperplasia, the one pelvic condition of proved estrogenic origin. Endometrial hyperplasia was present in only 11 of 40 women (27.5 per cent) who were curetted at the time of removal of the polyps. Nine of these 11 patients with coexisting endometrial hyperplasia were, moreover, in the fifth decade of life, when the incidence of endometrial hyperplasia, independent of other genital lesions, is ordinarily high.<sup>10</sup> The finding of an atrophic endometrium in 11 additional patients (27.5 per cent), all of post-menopausal age, emphasizes the widely diversified endometrial patterns found in association with cervical polyps and the nonendocrine etiology of the condition (Table III).

TABLE III. ENDOMETRIAL PATTERN IN 40 PATIENTS WITH CERVICAL POLYPS

ENDOMETRIUM	NUMBER OF PATIENTS	PERCENTAGE
Hyperplastic	11	27.5
Hypoplastic (atrophy)	11	27.5
Premenstrual (secretory)	10	25.0
Decidua	5	12.5
Proliferative (interval)	3	7.5

#### PATHOLOGY

The term cervical polyp includes all wholly or partially pedunculated tumors of the cervix, which often tend to project into the vagina on a long pedicle. Usually, they arise as mucous polyps from the endocervix near the internal os. A characteristic feature of the microscopic appearance of a cervical polyp is the fidelity with which the structure of the endocervix is reproduced. The histologic architecture of the cervical polyp is always more or less altered by the presence of certain secondary pathologic changes which, in the present group, included inflammation, cyst formation, epidermization, carcinoma, decidual reaction, edema, and excessive fibrous tissue (Table IV).



TABLE IV. INCIDENCE OF SECONDARY PATHOLOGIC ALTERATIONS IN THE CERVICAL POLYPS OF 117 PATIENTS

HISTOLOGIC PATHOLOGY OF POLYP	*NUMBER OF PATIENTS	PERCENTAGE
Inflammation	81	69.2
Cyst formation	14	11.9
Epidermization	10	8.5
Fibrous	9	7.6
Edema	4	3.4
Decidual reaction	3	2.5
Carcinoma	2	1.7

\*The total number is more than 117 in this table because more than one of the histologic changes coexisted in several patients.

*Chronic inflammation*, recognized by diffuse or localized collections of lymphocytes and plasma cells, is unquestionably the most common histologic picture encountered in cervical polyps. It was present in 81 of the 117 specimens (69.2 per cent). The protrusion of the cervical polyp through the external os, interfering with its blood supply and exposing it to friction, predisposes it to ulceration and infection. The inflammatory reaction, always more acute at the tip of the polyp, usually includes polymorphonuclear leucocytes in areas where the surface epithelium had been lost.

The columnar epithelium covering the surfaces and lining the glands of a cervical polyp is susceptible, in common with the epithelial elements of the endocervix as a whole, to substitution by stratified squamous epithelium. This benign process, known as *epidermization*, is especially likely to occur in cervical polyps because of exposure, ulceration, and infection. The exact pathogenesis of epidermization in endocervical polyps is unknown. Clarification of the problem is hampered by our ignorance concerning many of the factors involved in the growth of cells. At least five theories have been formulated to account for the mechanism of epidermization, the simplest of which regards the process as the result of growth of basal cells from either adjacent squamous epithelium or subjacent squamous cell-rests.<sup>11</sup> It is probably, as Meyer<sup>12</sup> suggests, a reparative process. The conception that epidermization represents a true metaplasia, implying the actual conversion of mature columnar cells into squamous epithelium, is open to question.

While divergent views are held concerning the exact origin of epidermization in cervical polyps, unanimity of opinion exists regarding its ordinarily benign character.<sup>12, 13</sup> The presence, however, of slightly atypical squamous epithelium in unexpected cervical quarters may lead to confusion in diagnosis and unnecessary radical operations. The protean character of epidermization makes this possibility more real than theoretical. Happily, such errors may be avoided by careful application of the well-known cellular criteria of malignancy and by the knowledge that carcinoma, in contradistinction to epidermization, occurs infrequently in cervical polyps.

In the present series of 117 patients with cervical polyps, two instances (1.7 per cent) of squamous cell *carcinoma* were found. In each, the diagnosis rested not only on the presence of heterotopic epithelium, but also on the atypic characteristics of the malignant cells, namely, hyperchromatism, totally irregular nuclei, and loss of polarity. Summaries of the histories of the two patients with carcinomatous polyps follow:

CASE 1.—(Mount Sinai Hospital, No. 88939.) Mrs. D. B., white secundipara, aged 48 years, was admitted for the sole complaint of slight intermenstrual bleeding of eight months' duration. Examination revealed no gynecologic abnormalities other than the presence of a friable, acorn-sized, endocervical polyp with a wide base. Treatment included cervical amputation, diagnostic curettage, intrauterine application of 2,400 mg. hr. of radium, and three courses of roentgen irradiation to the pelvis during the ensuing eighteen months. Histologic

study of the specimen showed, in addition to epidermization, a localized squamous cell carcinoma at the base of the polyp. The patient has remained perfectly well for six years.

CASE 2.—(Mount Sinai Hospital, No. 73066.) Mrs. R. R., white, quadripara, aged 50 years, was hospitalized because of profuse leucorrhea and slight metrorrhagia of three months' duration. Pelvic examination disclosed the presence of several pea-sized endocervical polyps. Treatment included multiple polypectomy and application of 2,400 mg. hr. of radium to the cervical canal. Microscopic study of the polyps showed some degree of epidermization in all and a squamous cell carcinoma at the tip of one. The patient has also remained perfectly well for six years.

#### TREATMENT

In the group of 117 patients herein reported, polypectomy was performed in 99 (84.6 per cent) and cervical amputation in the remaining 18 (15.4 per cent). Other surgical procedures for conditions unrelated to cervical polyps were executed in some of the patients (Table V).

TABLE V. SURGICAL MEASURES EMPLOYED, IN ADDITION TO POLYPECTOMY AND CERVICAL AMPUTATION, IN 117 PATIENTS WITH CERVICAL POLYPS

	NUMBER OF PATIENTS	CAUTERIZATION	CURETTAGE		SUBTOTAL HYSTERECTOMY
			WITH RADIUM	WITHOUT RADIUM	
Polypectomy	99	*68	6	39	6
Cervical amputation	18	0	3	15	0
Total	117	68	9	54	6

\*This number includes several patients of the curettage and hysterectomy groups and, also, an additional patient who had an oophorectomy for cystadenoma.

Cervical polypectomy may be readily and safely accomplished, as observed in this study, by purposeful torsion of the pedicle or by excision with scissors, scalpel, or wire snare. Whenever possible, in either method, the base of the polyp should be clearly visualized and cauterized with the electric cautery. The latter procedure is a most useful adjunct to polypectomy, because it not only accomplishes hemostasis but also eradicates any infection lurking at the base of the polyp. Cauterization was employed in 68 of the 99 patients (68.6 per cent) who had polypectomies. A temporary but severe flare-up of a supposedly quiescent pelvic inflammation followed the polypectomy and cauterization in one of the 68 patients. This experience serves to stress the fact that unexpected disastrous results occasionally follow even minor cervical procedures when the presence of smoldering salpingitis is not recognized.

Intrauterine curettage, with or without the application of radium, is frequently indicated at the time of polypectomy because abnormal uterine bleeding is, as aforementioned, not always clearly explained by the presence of an innocuous-appearing cervical polyp. This is especially true in women at or just beyond the climacteric, an age when both benign uterine bleeding and carcinoma of the uterine body are most often encountered. Intrauterine application of radium was employed in 9 patients of the present series because the bleeding could not be explained on the basis of polypoid alone.

No physician is justified in assuming on the basis of macroscopic appearance alone, that a cervical polyp is benign. Neither the fact that only 1.7 per cent of such polyps are malignant nor the financial consideration involved in routine histologic studies can ease the "burden of responsibility" from the physician who carelessly discards a cervical polyp. Moreover, the entire polyp should be thoroughly examined, since early carcinoma is, as illustrated by the two instances cited previously, a localized process. The mere suspicion of malignancy warrants the use of radium irradiation and demands close scrutiny of the patient's future course.

## RECURRENCE

Only 104 of the 117 patients herein reported were successfully followed for periods varying from one to seven years. The follow-up examinations, conducted by the respective operators, did not reveal a single recurrence of cervical polyp in the group of 104 women.

## SUMMARY

The clinical and pathologic features of cervical polyps, as encountered in 117 patients, are presented. It is shown that the etiology of a cervical polyp cannot be ascribed to an endocrine disorder and that it is more likely an independent neoplastic process with some relationship to the trauma of childbirth.

The importance of a careful histologic study of removed cervical polyps is emphasized because the tendency to epidermization, or substitution of the columnar epithelium by stratified squamous epithelium, may lead, when misinterpreted, to either overlooking of a squamous cell carcinoma or a useless radical operation.

The histories of two patients (1.7 per cent) who had carcinomatous polyps are related.

The follow-up studies of 104 of the 117 patients indicate the relative infrequency of recurrence of cervical polyps removed either by polypectomy or by cervical amputation.

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Experiments were carried out on the interruption and inhibition of early pregnancy by the oral administration of two new estrogens, ethynyl estradiol and diethylstilbestrol. The former is a derivative of estradiol, the latter, a synthetic substance, not quite as effective. Both of these substances given orally inhibit the effect of progesterone and prevent the implantation of the blastocysts in rabbits. Small doses of the synthetic product prevent implantation in rats, and ethinol estradiol interrupts early pregnancy in rabbits. The application of these substances for similar purposes in women is as yet problematic. Theoretically the results of their administration should be the same, although the period of their effectiveness would be relatively much shorter than in rabbits.

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## PREGNANCY AFTER THORACOPLASTY FOR TUBERCULOSIS

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IN A PREVIOUS paper<sup>1</sup> we presented a study of pregnancy, labor, and the puerperium in patients who received collapse therapy for pulmonary tuberculosis at Herman Kiefer Hospital. This investigation was concerned with artificial pneumothorax and phrenic nerve operations, and did not include thoracoplasty. Among 144 women of all ages who received collapse therapy by thoracoplasty operations while on the tuberculosis service of this hospital, we were able to trace the records of 10 who later became pregnant one or more times. In view of the increasing use of this operation, particularly in young women, it was thought that a study of the results in these cases, combined with a review of the literature, should yield information of value not only to the obstetrician, but also to the phthisiologist and the thoracic surgeon.

The production of pulmonary collapse by the extensive operative procedure of thoracoplasty has, as a rule, been confined to those tuberculous patients with advanced lesions who have shown little or no favorable response to more conservative treatment. The results, as reported from this hospital<sup>2</sup> and elsewhere, have been so generally satisfactory as to mark a distinct advance in the treatment of serious tuberculosis. The very fact, however, that such extreme measures were necessary for the control of the pulmonary condition would seem to be sufficient contraindication to the strain of childbearing with its possible effect on the tuberculosis. Moreover, it has been suggested that the restriction of respiratory exchange due to the collapse might prevent proper development of the pregnancy, or perhaps with the extra load of pregnancy and labor might dangerously exceed the cardiac capacity. Jameson,<sup>3</sup> on the basis of 11 case reports in the literature, states, "As far as the risks of childbirth are concerned, it would seem that one should fear the possibilities of respiratory embarrassment during labor more than the likelihood of the tuberculosis being reactivated."

In addition to those cited by Jameson, we have found the following reports in the literature.

Alberts<sup>4</sup>: A 25-year-old primigravida who had had unilateral tuberculous for five years when a thoracoplasty was done. She was delivered eleven months later, after a one-and-one-half-hour labor, of a 7-pound child. She had done heavy work during pregnancy, and had received no special care. She nursed her baby for fifteen months, and at the end of that time there was no activity on the affected side or extension to the other.

Vannucci<sup>5</sup>: A 21-year-old patient in 1928 was found to have tuberculosis of the upper one-third of the right lung, and a small area at the left apex. Thoracoplasty operations were done on the right side in February and September, 1930. She was delivered in January, 1933 of a normal child which was breast fed. During pregnancy there was a loss in weight of 5 kilograms. X-rays in September, 1933 showed no definite ill effect on the pulmonary condition.

Amorin<sup>6</sup>: A 21-year-old woman with ulcrofibrotic involvement of the whole left lung became pregnant while improving under treatment. Thoracoplasty was done in two stages, at the second and sixth months, with no postoperative trouble. Delivery of a 2,700 gm. child occurred at term. The child did well on mixed breast and artificial feeding. During pregnancy there was continued improvement. Amorin believed the results in this case to be a potent argument against therapeutic abortion for tuberculosis. He found only two previous reports of thoracoplasty during pregnancy, namely, those of Sayé in 1924, and Rist in 1926.

Boquist, Simons, and Myers<sup>7</sup>: After seven years of treatment for tuberculosis, including a two-stage thoracoplasty done in May, 1922 and September, 1923, the patient was discharged from the hospital in March, 1924. She was delivered in March, 1929 by midforceps operation after a four-hour-and-twenty-minute labor. The baby was normal, and the puerperium uneventful. In the last month of pregnancy there was considerable dyspnea, and during labor this became extreme with pulse rate up to 130 or 140 per minute. With active care of the baby and housework there was reactivation of the disease a little less than a year after delivery, which required sanatorium care for a year.

Blisnjanskaja and Lasarevitch<sup>8</sup>: Reported the case histories of 7 women who had become pregnant following thoracoplasty which had been done after other collapse therapy had failed to control advanced tuberculosis.

1. Delivery four years after thoracoplasty. The child was premature, weighing 1,800 gm., but lived. The mother was well six years later when an abortion was induced.

2. Term delivery of a 3,600 gm. child two years and two months after thoracoplasty. There was no marked reactivation of the disease until two years after pregnancy when there was exacerbation with hemoptysis.

3. Low forceps delivery of a 3,500 gm. child three and one-half years after a thoracoplasty operation. The patient was working when hemoptysis occurred one year and five months after delivery.

4. The first child was born fifteen months following thoracoplasty. Some exacerbation of the disease occurred. During the second pregnancy (five years after thoracoplasty) there was hemoptysis at seven months. The child weighed 3,200 gm. Reactivation of the tuberculosis occurring nine months after delivery was ascribed to "arduous circumstances" rather than pregnancy.

5. Two years after thoracoplasty, therapeutic abortion was done because of reactivation of the tuberculosis. A year later the patient was delivered by low forceps of a 2,500 gm. child. There was again reactivation of the disease, but the patient was doing well eighteen months after delivery.

6. Delivery of a child weighing 3,700 gm. about two years after thoracoplasty operation. The patient was in good condition eighteen months later. An abortion occurred several years later.

7. Six months after thoracoplasty a therapeutic abortion had been done. Two years later, the patient had had a spontaneous premature labor at thirty-six weeks which followed a fall from a chair. The child died the second day. Five months post partum there was no evidence of reactivation.

From their experience, these authors conclude that when thoracoplasty gives good results, pregnancy may be allowed if living conditions are good. On the contrary, if the tuberculosis is subcompensated for by the operation, pregnancy should be interrupted. Delivery should be operative in the second stage of labor to avoid the strain of expulsive efforts.

Guillemin and Chabeaux:<sup>9</sup> The 22-year-old woman in her second pregnancy had previously been treated satisfactorily by phrenicectomy. The last menstrual period began on March 11, 1936. Examination in July showed the pulmonary condition worse. A three-stage thoracoplasty done in August was without complications. She was delivered Dec. 19, 1936, of a rather small child. A year after delivery the patient was in good health and gaining weight while active in her housekeeping.

Table I gives the salient features in our 10 cases. It will be noted that the first two patients had interruption of the pregnancy in the early months. Both were treated at other hospitals. The first was apparently an instance of curettage for incomplete abortion. In the second case it is uncertain whether or not reactivation of the tuberculosis was the indication for therapeutic abortion. Although several of the remaining 8 patients were not delivered at this hospital, sufficient data for our investigation were obtainable.

Our 8 cases in which pregnancy was allowed to proceed plus those reviewed by Jameson<sup>3</sup> and those from the literature, abstracted by us, make a group of 31 patients for study. The possible ill effects of pregnancy on the mothers should be indicated by the number who died or whose tuberculosis became worse during pregnancy or during a period of one year after delivery. It will be noted that some patients in the group were not observed for a full year post partum. However, this number was too small to affect the conclusions which may be drawn from Table II.

Table II shows that 6 out of 31, or about one out of five, patients with thoracoplasty for tuberculosis who became pregnant had serious exacerbation. It is recognized that patients with advanced tuberculosis (even though it be arrested) may have reactivation of the disease. However, reactivation in these cases seemed to bear a relationship to childbearing. A possible exception is our patient who died, since in addition to active involvement of the other lung and tuberculous pneumonia, she had amyloid disease of the kidneys which may well have antedated the pregnancy. The other 5 patients with exacerbations responded to treatment after delivery.

It is interesting that two of our patients went through a second pregnancy without trouble in either. A patient reported by Blisnjanskaja and Lasarevitch was not so fortunate. She had two full-term pregnancies with exacerbations during each. Another, after a therapeutic abortion because of reactivation of the disease, had a child five years after thoracoplasty with hemoptysis during pregnancy and definite exacerbation nine months following delivery.

It is also of considerable interest that thoracoplasty has been successfully performed during pregnancy in at least four instances (Sayé, Rist, Amarin, and Guillemin and Chabeaux). It would seem from this that the procedure might be seriously considered for those few pregnant tuberculous patients who do unsatisfactorily even with artificial pneumothorax or phrenic nerve operation.

In regard to the accuracy of the statistics shown in Table II, it may be of significance to note that 4 of the 6 cases with unfavorable results occurred in the two series (15 altogether) reported by Blisnjanskaja and Lasarevitch and by us, or 2 out of 7 and 2 out of 8 cases, respectively. This apparent discrepancy in results may be due to the small numbers of cases involved, though the possibility exists that the tendency in single case reports has been toward publishing only the good results. If the latter is the case, the expectation of unfavorable outcome for these patients should be considerably greater than indicated in Table II.

TABLE I. HERMAN KIEFER HOSPITAL CASES OF PREGNANCY AFTER THORACOPLASTY

AGE, RACE, PARITY	THORACO- PLASTY	DELIVERY OR ABORTION	DURA- TION OF PREG- NANCY	SPONTA- NEOUS OR OPERA- TIVE	CHILD	TUBERCU- LOSIS IN PREG- NANCY	COMPLI- CATIONS IN PREG- NANCY AND LABOR	CONDITION AFTER DELIVERY
L. B. Age 22 White Grav. iv	April and June, 1933	July 13, 1934	10 wk.	Operat. abortion (no fetus)	--	No change?	None	August, 1938. Working, tuberculosis arrested
V. Mc. Age 29 White Grav. ii	Feb. and March, 1932	Jan., 1936	8 to 12 wk.	Operat. abortion	--	No change?	Weak- ness, nausea	Sept., 1938. Weak, losing weight
M. W. Age 26 White Grav. i	Feb. and March, 1934	July 6, 1936	20 wk.	Spont.	1 lb. Macer- ated	Active on other side Tubercu- lous pneu- monia	Amyloid kidneys Uremia	Died 5 days post partum
R. F. Age 22 White Grav. i	Feb. and March, 1934	Jan. 19, 1936	34 wk.	Spont.	4 lb. 6 oz. Died 16 days	No Change	None	April, 1937. Marked tuber- culosis of other side
E. S. Age 29 White Grav. ii- iii	March and May, 1933	June, 1935 Feb., 1937	Term  2 to 3 mo.	Spont.  Spont.	6 lb. 12 oz. Well	No change	None	June, 1938. No progres- sion. Active at home
L. M. Age 30 Negro Grav. vi	June to Sept., 1932	Aug. 21, 1935	Term	Spont.	6 lb. 7 oz.	No change	None	Dec., 1937. No progres- sion. Feels well
E. P. Age 26 Negro Grav. vi	May, 1933, to July, 1935	Dec. 18, 1937	Term	Spont.	5 plus lb. Well	No change	None	July, 1938. Afebrile, spu- tum neg.
L. H. Age 16 White Grav. i-ii	Feb. and June, 1930	March, 1936 Oct., 1937	Term  Term	Spont.  Spont.	5 lb. 10 oz. 6 lb. 12 oz. Both well	No change No change	Bron- chitis Dyspnea None	Sept., 1938. Well, active at home
J. L. Age 30 White Grav. vi- vii	Oct. to Dec., 1930	Feb., 1933 March, 1935	Term  Term	Spont.  Spont.	7 lb. 8 oz. 6¼ lb. Both well	No change Same	None None	Oct., 1938. Well after both preg- nancies
H. H. Age 26 White Grav. i	Feb. to April, 1933	June, 1935	Term	Low forceps	8 lb. 9 oz.	No change	None	August, 1938. 5 months preg. No progression

Fears as to the dangers from respiratory difficulty during pregnancy and labor are not borne out by the records in these cases. The 31 women had a total of 34 pregnancies which were prolonged to at least five months. In only 3 instances was mention made of dyspnea during pregnancy or labor. With our patient this was present only during pregnancy and was not troublesome. Dyspnea was considerable, however, in the cases reported by Mueller and by Boquist, Simons, and Myers.

TABLE II. MATERNAL RESULTS FOR PATIENTS WHO HAD THORACOPLASTY AND ONE OR MORE PREGNANCIES

(Showing the deaths and the number whose tuberculosis became worse during pregnancy or in the year after delivery)

UNAFFECTED	WORSE DURING PREGNANCY	WORSE POST PARTUM	DIED	TOTAL
25	1	4	1	31

Moreover, in the latter case the dyspnea reached a serious degree during labor. We have found no record of induction of premature labor because of dyspnea, intractable vomiting, or other complication due to thoracoplasty.

The possible effect of thoracoplasty on the outcome of pregnancy is of importance. In the 34 pregnancies occurring among these 31 women there were 5 spontaneous premature labors or late abortions. This rather high incidence approximated that found by us<sup>1</sup> among the tuberculous patients of our previous investigation—regardless of whether or not they had received collapse therapy or other treatment, or no treatment at all. Consequently, the excess of the rate over that for the non-tuberculous patients in this hospital seemed attributable to the tuberculosis itself. With the patients having thoracoplasty, it also appears possible that the disease rather than the consequences of the operation was responsible for at least some of the premature interruptions. Although Blisnjanskaja and Lasarevitch believed that the cause in one of their cases was a fall from a chair, our two instances occurred in the only patients showing exacerbation of the tuberculosis. There was no evident explanation for the other two cases found in the literature. The only fetal or neonatal deaths reported for these 34 pregnancies were the 3 which occurred among the 5 children born prematurely.

#### DISCUSSION

During recent years the necessity for therapeutic abortion for various medical conditions has been decreasing as therapeutics for the conditions requiring it has improved. We refer particularly to pregnancy complicated by such conditions as pernicious vomiting, toxic thyroid, heart disease, diabetes, and the milder arrested forms of pulmonary tuberculosis. In accord with this tendency it seems possible that therapeutic abortion can also be resorted to less frequently in other forms of tuberculosis, even in cases so far advanced as to require thoracoplasty for control. With the increasing use of this procedure, the problem of whether or not to allow a woman so treated to continue with her pregnancy will appear more frequently.

So far as we have been able to ascertain, actual experience with this situation has been very limited up to the present. An examination of the medical literature has revealed only one small series of 7 cases and scattered cases to the number of 16 (with data sufficient to be of value). These with 8 cases reported herewith, make a group of 31 for study.

The 31 women had 34 full-term or premature deliveries. One mother died and 5 others had serious exacerbation of the tuberculosis during pregnancy or within one year after delivery. As explained before, we doubt that these figures show quite the true expectation for trouble. They probably do indicate, however, that the majority of women may safely go through pregnancy after thoracoplasty. Nevertheless, risks for some are definitely greater than admitted by the more optimistic.



Complicating respiratory difficulty was mentioned in three cases, though this was serious (not fatal) in but one. Two patients went through 2 full-term pregnancies safely, though a third woman had exacerbations in both.

It is noteworthy that thoracoplasty has been done successfully during pregnancy in at least four instances.

We found no definite evidence that thoracoplasty had deleterious effects on pregnancy. There was a rather high incidence of premature labors, but this was in accord with our previous findings in tuberculous women regardless of the type of treatment. The 3 fetal deaths in this group occurred among premature babies.

We are indebted to the members of the Departments of Tuberculosis and Thoracic Surgery for many helpful suggestions in the preparation of this paper.

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## A COMPARATIVE STUDY OF MALE AND FEMALE PELTS\*

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**I**N A recent communication<sup>1</sup> we reported the results of a roentgenologic study of the size and shape of the pelvic inlet in 582 primigravid white (clinic) women, 104 nulliparous student nurses from a somewhat different racial stock and a more privileged economic class, and 107 young girls who ranged in age from 5 to 15 years. The pelves of this group were classified according to the Thoms' system of classification, which is based on the relative lengths of the transverse and anteroposterior diameters of the pelvic inlet as follows:

*Dolichopellic or Anthropoid Type:* The transverse diameter is less than the anteroposterior diameter.

*Mesatipellic or Round Type:* The transverse diameter either equals the anteroposterior diameter or exceeds it by no more than 1 cm.

\*This investigation was aided by grants from the Fluid Research and Teaching Funds of Yale University School of Medicine and the General Education Board of the Rockefeller Foundation. Dr. Hugh M. Wilson, Associate Professor of Radiology, Yale School of Medicine, kindly made available to us the necessary radiologic facilities for this study.

*Brachypellic or Oval Type:* The transverse diameter exceeds the anteroposterior by from 1.1 to 2.9 cm.

*Platypellic or Flat Type:* The transverse diameter exceeds the anteroposterior by 3 cm. or more.

This classification we have used in clinical practice during the past four years, and it appears to be of greater usefulness and of more ready comprehension than any other classification with which we are familiar. Nevertheless, for certain comparisons a classification based upon the pelvic index, as suggested by Turner,<sup>2</sup> is also of usefulness, as will be noted later.

The incidence of the various types of pelvis in these 686 adult white women is shown in Table I.

TABLE I

TYPE	582 CLINIC WOMEN PER CENT	104 STUDENT NURSES PER CENT	TOTAL 686 ADULT PER CENT
Dolichopellic	15.0	37.5	18.4
Mesatipellic	44.8	44.2	44.7
Brachypellic	34.3	18.2	31.8
Platypellic	5.6	--	4.7

These findings are of considerable interest if we compare them with what is described as the "normal" female pelvis in textbooks of anatomy. In such texts we find the normal female pelvis described as one in which the transverse diameter of the inlet exceeds the anteroposterior diameter by more than 2 cm. On the basis of this criterion we find that only 14.9 per cent of the clinic women and 5.7 per cent of the student nurses possess this type of pelvis. Obviously the prevailing concept of the "normal" pelvis of white women needs revision, a matter which we have previously discussed.<sup>3</sup>

In order to be adequate for clinical purposes a survey of the pelvis cannot be limited to a study of the inlet alone, but it must include a description of the remainder of the pelvis as well. During the past year, using improved techniques, we have made such a survey of 200 white women. It is our opinion that not only is the shape of the various segments of the pelvis of importance but that certain diameters are equally important. These diameters are:

Pelvic Inlet	{ 1. Anteroposterior diameter 2. Transverse diameter 3. Posterior sagittal diameter
Midpelvic Plane	{ 1. Anteroposterior diameter 2. Transverse diameter (interspinous) 3. Posterior sagittal diameter
Pelvic Outlet	{ 1. Transverse diameter 2. Posterior sagittal diameter (intertuberal)

For a further discussion of these diameters and the points from which they are estimated, the reader is referred to a recent communication by one of us.<sup>4</sup>

In the present paper we wish to report the results of an x-ray study of the pelves of 69 white adult male students, a group which resemble very closely the student nurses of our previous series both in economic level and in national derivation. Such a survey has a distinct clinical interest due to the fact that certain features regarded as characteristically male may occur in female pelves, a fact which has been known for many years and which has recently been emphasized by Caldwell and Moloy.<sup>5</sup> Such occurrences may have pronounced obstetric importance, and may be the cause of severe dystocia.

In the first consideration of this survey of the male pelvis, we would call attention to the description of the "normal" male pelvis as found in anatomic texts. In general the male pelvic inlet is said to be heart-shaped and to have an anteroposterior diameter which is smaller than its transverse. A comparative study of our findings may be stated in terms of the pelvic index ( $P.I. = \frac{A.P. \times 100}{Trans.}$ ).

Trans.

The average pelvic index of our group was 100.5. This is considerably higher than the index of 80.8, the average reported for European males, by Turner (77.0), Verneau (80.0), Topinard (80.0), and Krause (84.4), whose figures are still cited as typical of white males in modern textbooks of anatomy. Only two of the 69 men in our series had a pelvic index of less than 85 (77.0 and 84.8).

According to the Thoms' classification, the occurrence of pelvic type in the group was as follows:

Dolichopellic type	20 instances or 28.9%
Mesatipellic type	34 instances or 49.2%
Brachypellic type	15 instances or 21.7%

Thus, it is seen that in male pelves, as in female pelves, these basic pelvic types appear. In this limited series the percentage ratio is not greatly unlike that of the student nurse group given above.

The various average pelvic diameters observed in the 69 males and the 200 females of our present series are listed in Tables II and III, in which cases are arranged according to pelvic type.

TABLE II. MEAN VALUES FOR PELVIC TYPES IN 200 WHITE WOMEN

TYPE	INLET			MIDPLANE			OUTLET	
	A. P.	TRANS.	P. S.	A. P.	TRANS.	P. S.	TRANS.	P. S.
Dolichopellic	12.50	11.72	5.07	12.55	9.45	5.22	8.95	7.84
Mesatipellic	11.75	12.32	4.48	12.34	10.34	5.23	9.16	7.71
Brachypellic	11.06	12.67	4.15	12.01	10.32	5.23	8.92	8.05
Platypellic	9.0	12.67	2.75	11.67	10.45	4.71	9.12	7.58

TABLE III. MEAN VALUES FOR PELVIC TYPES IN 69 WHITE MALES

TYPE	INLET			MIDPLANE			OUTLET	
	A. P.	TRANS.	P. S.	A. P.	TRANS.	P. S.	TRANS.	P. S.
Dolichopellic	12.30	11.60	4.89	12.43	8.54	4.47	10.65	7.68
Mesatipellic	11.46	11.87	4.01	12.07	8.66	4.22	10.75	7.49
Brachypellic	10.77	12.01	3.63	11.96	8.86	4.33	10.72	6.97

The above figures show that in each pelvic type the male pelvis has a smaller capacity than that of the female. The diameters which designate the chief differences are the bispinous and the three posterior sagittals. The male pelvic inlet as it occurred in our series is not

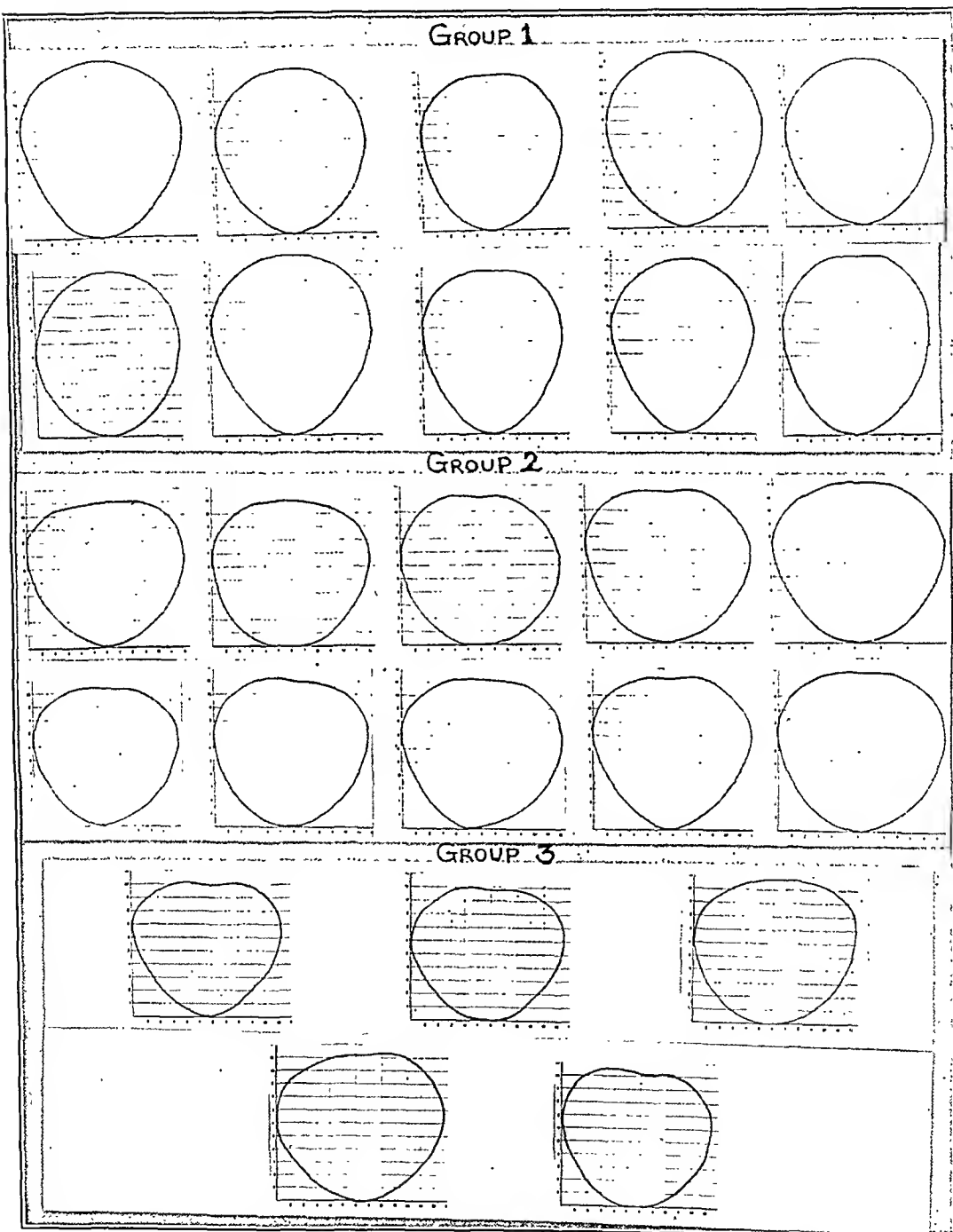


Fig. 1.—Group I, representative tracings of pelvic inlets of the dolichopellic or anthropoid group. Group II, representative tracings of pelvic inlets of the mesatipellic or round group. Group III, representative tracings of pelvic inlets of the brachypellic or oval group.

greatly different from that of the female. The term "heart-shaped" would be a very inappropriate designation for the inlet of the great majority of these male pelvises. This is evident from the tracings of the inlet of representative pelvises shown in Fig. 1. Attention also is directed especially to the forepart of the pelvic inlet. As will be seen in most instances, this is not angular but a sweeping curve and is not greatly unlike that seen in most female pelvises. The relative shortening of the posterior sagittal diameter of the inlet, which is said to be so characteristic of the male pelvis, is not marked in our series, an average of approximately 0.5 cm. less than the figures for the female series.

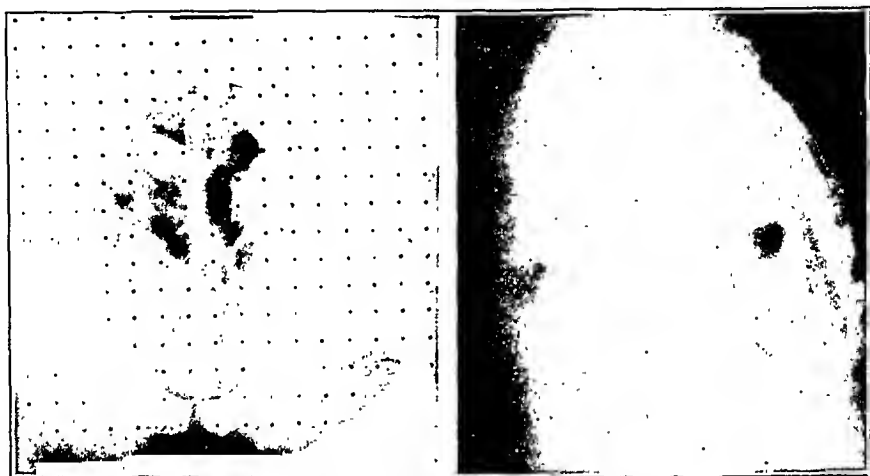


Fig. 2.—Dolichopellic or anthropoid type of male pelvis. Lateral view shows typical male notch, and the sacrum is composed of six segments.

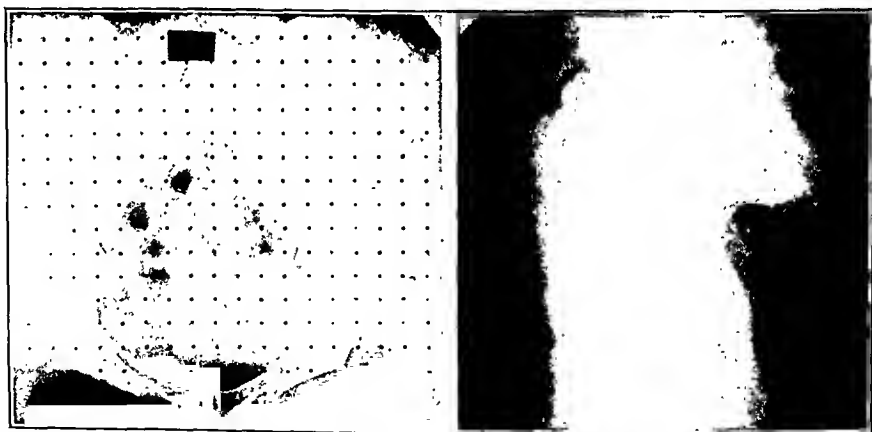


Fig. 3.—Mesatipellic or round type of male pelvis.

The most typical male characteristics in pelvic contour in our series were the shape of the sacrosciatic notch and the angle formed by the pubic rami. The sacrosciatic notches showed typical male features in all subjects examined, although in a few cases a wideness was present to the extent that the female type was suggested. The subpubic angle was not studied roentgenologically in all cases, but in those in:

which this was done it was found to be typically masculine. A word should be added concerning the bituberal or outlet transverse diameters given above. In the women this diameter was determined by palpation, but in the male series it was determined by x-ray. The findings show clearly the result of the lack of uniformity in designating that part of the tubera ischii from which measurements should be taken and suggest studies to correct this error. Because of these discrepancies the intertuberal diameters of the two groups are not comparable.

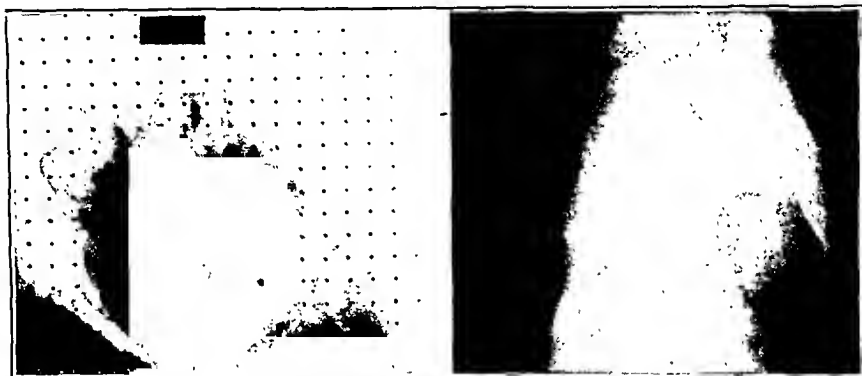


Fig. 4.—Brachypelvic or oval type of male pelvis.

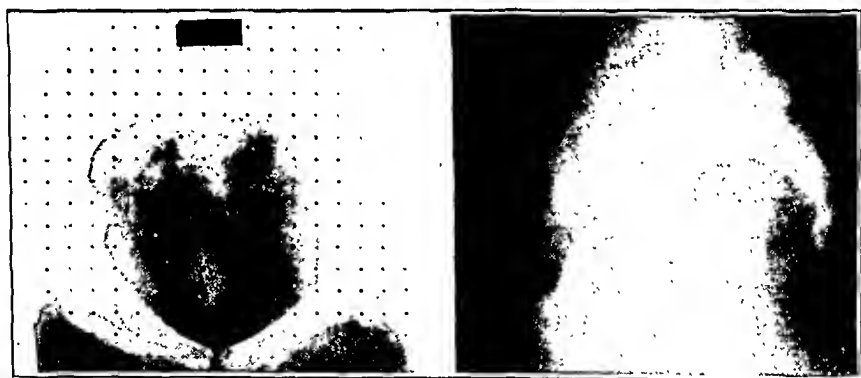


Fig. 5.—The pelvis inlet shows a tendency to the "heart-shape." The sacrum in its lateral aspect shows changes suggestive of rachitic influence.

A study of the sacrum in this series as seen in its lateral aspect revealed the presence of six segments in 9 instances (so-called high assimilation). These were equally divided in the three types, although in our opinion this variation is more often seen in association with the dolichopelvic type pelvis in women.

A study of the curve of the anterior sacral surface from above downward showed the usual deviations from a normal sweeping curve, which we also noted in our female series. In seven instances the upper two-thirds of the anterior sacral surface showed a lack of the usual concavity with the exaggeration of the forward curve of the lower one-third of this surface. In two instances the entire anterior surface

of the sacrum was straight or convex in its lateral outline from above downward, and the inlet in these cases showed a definite tendency to the heart-shaped form with relatively shortened posterior sagittal diameters (3.3-3.3), Fig. 5. These sacral findings strongly suggest to us changes due to rachitic influence.

We may summarize our findings in this comparative study of male and female pelves as follows:

1. The pelvic bones in males are heavier than those found in females, and in general the whole pelvis of the former has a more angular appearance.

2. The pelvic inlet in males appears in general more circular, and the posterior sagittal diameter in this plane is slightly shorter than that seen in female pelves. This is due to a slight displacement posteriorly of the widest transverse diameter. The forepart of the pelvic inlet differs but slightly from that seen in female pelves and the so-called "heart-shaped" pelvic inlet was not characteristic of the great majority of pelves in our series.

3. The constant characters seen in male pelves were the structural heaviness and prominence of the ischial spines with narrowing of the pelvic side walls from above downward, the angular pelvic arch with a relatively narrow subpubic angle and the type of sacrosciatic notch which has been described as characteristically male.

4. The three main pelvic types which we have found in female pelves, i.e., dolichopellic, mesatipellic, and brachypellic, were also found to occur in male pelves.

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The prevention of ophthalmia neonatorum due to the gonococcus has been very widely provided for in laws and regulations of health departments. The instillation of silver nitrate solution at the time of birth has been most generally prescribed. Silver nitrate is a severe irritant to the conjunctiva and cornea and cases have occurred in which it has caused serious conjunctivitis when no gonococcal infection was present. Its use at too short intervals, more than one application in twenty-four hours, has also caused permanent opacities of the cornea.

Jackson feels that the more recent introduction of silver acetate as a safer and more widely efficient prophylactic should be welcomed by the profession. It would be particularly useful in sparsely settled districts where frequent renewal of the silver nitrate solution cannot be obtained without delay.

J. P. GREENHILL.

## AN INFANT INCUBATOR

### EMPLOYING CONTROLLED MIXTURES OF HELIUM AND OXYGEN TO COMBAT RESPIRATORY FAILURE

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UP TO the year 1938 many infants of diabetic mothers had experienced respiratory failure immediately after birth, the exact cause of which at that time seemed obscure but now appears to be related to a disturbed hormone balance. Prior to this knowledge it was suggested by one of us (P. W.) that helium-oxygen therapy might be of aid to such infants. For this purpose the incubator here described was constructed. The objectives of this incubator are to maintain the infant at the proper temperature and in an atmosphere containing only oxygen and helium. According to Alvan L. Barach,<sup>1</sup> to whom we are indebted for helpful suggestions and advice, a mixture of 20 per cent oxygen and 80 per cent helium has a measurably lighter density than room air and hence should require less effort in breathing on the part of the infant. Thus the aid to respiration is a mechanical one. Other investigators<sup>2</sup> have also reported beneficial effects of breathing helium-oxygen mixtures when respiration is embarrassed. Since the use of this chamber was started, the respiratory failure of newborn infants of diabetic mothers has been successfully prevented by prenatal hormone therapy. However, during the three years that this apparatus has been in use, a number of infants have been aided by being placed in the incubator, and the use of the equipment with other gaseous mixtures than the one originally proposed has proved helpful in some cases. In addition to its special feature of making it possible to determine and maintain the composition of the gaseous mixture in the chamber, this apparatus incorporates the four basic requirements of an incubator, namely, maintenance of proper temperature, maintenance of proper ventilation or oxygenation, maintenance of adequate humidity, and easy access to the infant without harmful exposure.

#### CONSTRUCTION OF APPARATUS\*

The chamber (Figs. 1 and 2) is made of galvanized sheet iron, its inside measurements being 56 by 30.5 by 23 cm. and its volume, 39.3 liters. The cover, which has a large plate glass window, fits into a water seal, making the chamber air-tight. A pipe at the top, *D* (Fig. 2) and another, *A*, at the diagonally opposite, lower corner facilitate thorough ventilation of the chamber and complete evacuation of the air in the chamber when it is to be filled with a gaseous mixture other than room air. The lower pipe has a metal screen in front of it, which prevents any obstruction of this pipe by bed clothing or pillows. The cover is held in place by two stout rubber bands, fastened securely on one side, drawn across the cover, and attached to snap hooks on the other side. The cover can be removed in two or three seconds by snapping up the hooks, throwing a lever operating a quick-throw release valve, *S*, which opens the chamber to the room, and lifting the cover by the two handles on its top. The chamber itself serves as a bassinet. The mattress is formed by inflating air pillows, which are placed in the bottom. By suitable combination these may

\*The construction of the chamber and the assembly of the apparatus were the work of V. Coropatchinsky of the Nutrition Laboratory.



be arranged as desired, to produce the proper tilt of the infant. The chamber is insulated on all sides by asbestos board, to prevent rapid changes of temperature. Heat is obtained from four 60-watt bulbs of the bung-hole type (*W-I* to *W-IV*), situated about 50 mm. below the bottom of the chamber. A piece of sheet metal halfway between them and the chamber aids in uniform distribution of the heat. The arrangement of the lamps is indicated in Fig. 2. The middle lamps are controlled by the thermostat, *U*, which maintains the temperature constant within 3° F. The two additional lamps permit rapid heating at the start or whenever, for any reason, it is desired to increase the temperature rapidly. Under ordinary conditions the thermostat adequately maintains the desired temperature. To indicate what the temperature conditions are, a thermometer, *T*, is located inside the chamber,

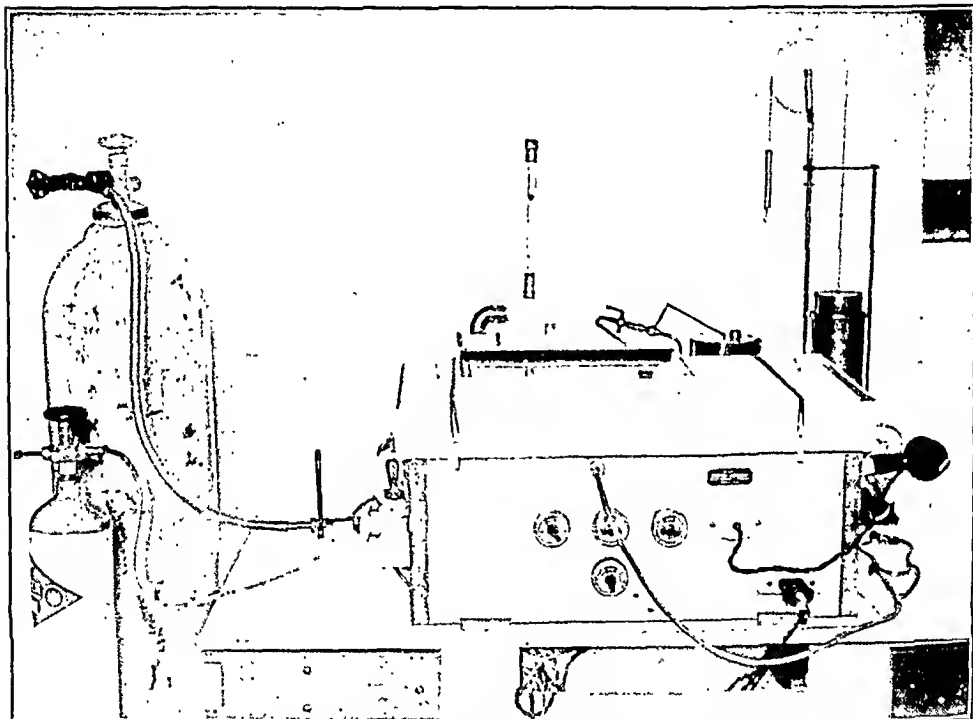


Fig. 1.—Incubator and respiration apparatus for continuous administration of a helium-oxygen mixture to infants.

being suspended from the cover. To insure that the heat transmitted through the bottom of the chamber does not become excessive, a brass tube closed at the end has been soldered into the side of the chamber. This tube fits into a fold in the rubber pillow and thus is not in the way. A thermometer, *TT*, which can easily be withdrawn a sufficient length to be read, is inserted in this tube.

The ventilation system, which is on the closed-circuit principle, consists of a centrifugal type, nonpositive blower,\* *B*, a soda-lime container, *C*, a flow meter, *R*, and necessary pipe connecting with the chamber. Flexible metal pipe was used for making the connections to the various instruments, as it was thought that rubber tubing might permit helium to escape by diffusion. Tests of one hour's duration, made since the construction of the apparatus, have indicated that rubber tubing will apparently hold helium satisfactorily. Provision for contraction and expansion of the air in the chamber is made through either the automatic filling device, *E*, or the calibrated, 1-liter spirometer, *K*, which is also used for testing the composition of the gaseous mixture. The carbon dioxide produced by the infant is absorbed from

\*Manufactured by Warren E. Collins, Inc., Boston, Massachusetts.

the ventilating air current by Wilson soda-lime, which also serves to maintain a high moisture content of the air. The capacity of the soda-lime container is approximately 3 liters, which is sufficient to remove the carbon dioxide produced by a new-born infant during 72 hours. The flow meter or "rotamesser" gives visual indication of the rate at which the air is being circulated through the chamber and is also used when the system is being filled with a gaseous mixture. The ventilation is usually maintained at 10 liters per minute.

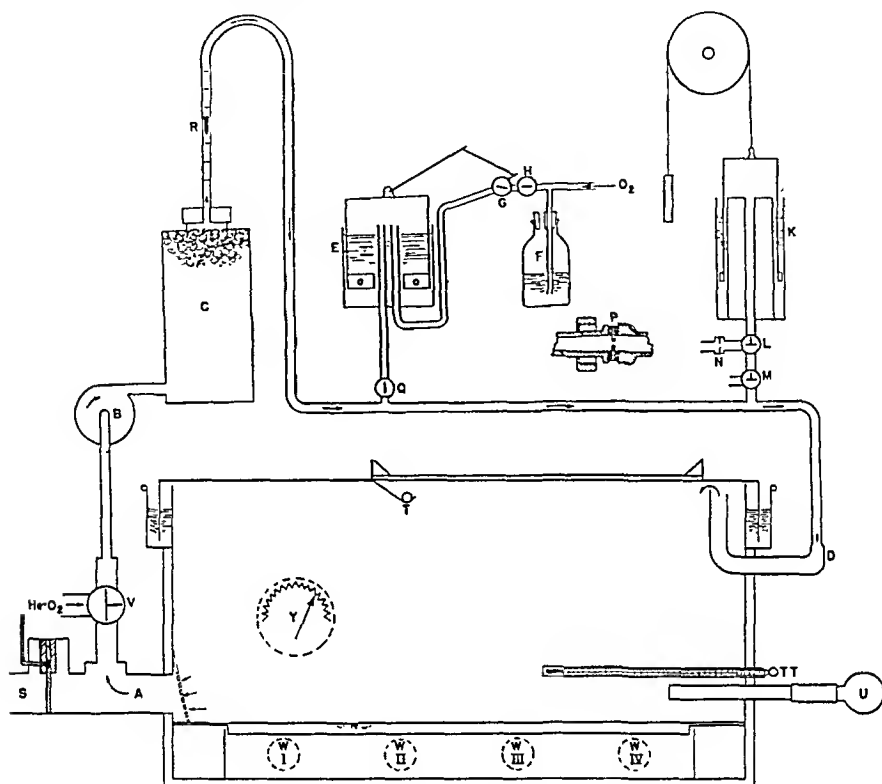


Fig. 2.—Schematic outline of incubator and respiration apparatus for continuous administration of a helium-oxygen mixture to infants. *A*, pipe for outcoming chamber air; *B*, rotary blower; *C*, container for soda-lime; *D*, pipe for ingoing chamber air; *W-I* to *W-IV*, electrical heating units; *U*, thermostat; *T* and *TT*, thermometers; *Y*, rheostat controlling speed of blower; *S*, release valve; *V*, valve for introduction of helium-oxygen mixture; *R*, flow meter indicating rate of flow of gas through ventilation circuit; *E*, automatic gas regulator acting also as expansion chamber; *o, o*, cork to compensate for weight of regulator bell; *F*, pressure-regulating bottle; *G*, valve through which oxygen enters regulator; *H*, valve used to disconnect gas regulator from oxygen supply; *K*, densimometer (1-liter spirometer) to determine composition of gaseous mixture in chamber; *L*, valve connecting densimometer with main ventilating air current or with orifice in disk *N*; *P*, enlargement of disk *N*; *M*, valve to connect densimometer with main ventilating air current or to connect a cylinder of gas with the densimometer or the chamber, as desired; *Q*, valve to close gas regulator *E* to main circuit.

*Method of Filling With Oxygen-Helium Mixture.*—It is desirable to replace the room air present at the start in the system and chamber as completely as possible with the helium-oxygen mixture, because any nitrogen in the chamber air will increase the density of the gaseous mixture and this in turn will necessitate more effort by the infant's lungs in breathing. This is effected by introducing at the inlet to valve *V* (which has been closed to pipe *A* and opened toward blower *B*) a mixture of 75 per cent helium and 25 per cent oxygen from a cylinder.\* With the

\*As mixtures of 75 per cent helium and 25 per cent oxygen can be obtained in 200 cu. ft. cylinders from the Ohio Chemical and Manufacturing Company, Cleveland, Ohio, this mixture is now used instead of the mixture of 80 per cent helium and 20 per cent oxygen employed in the preliminary studies.

valve *S* open and the valves *Q* and *M* closed to the ventilation system, the oxygen-helium mixture can be introduced first through the blower, soda-lime container, and connecting pipes and then into the top of the chamber through pipe *D*. As this mixture has a density considerably less than room air, it will stratify across the top of the chamber, if admitted at the proper rate, and (by displacement) will force the air in the chamber out through the openings *A* and *S* at the bottom. If the mixture is admitted at the rate of 20 liters per minute for 6 minutes, the air originally in

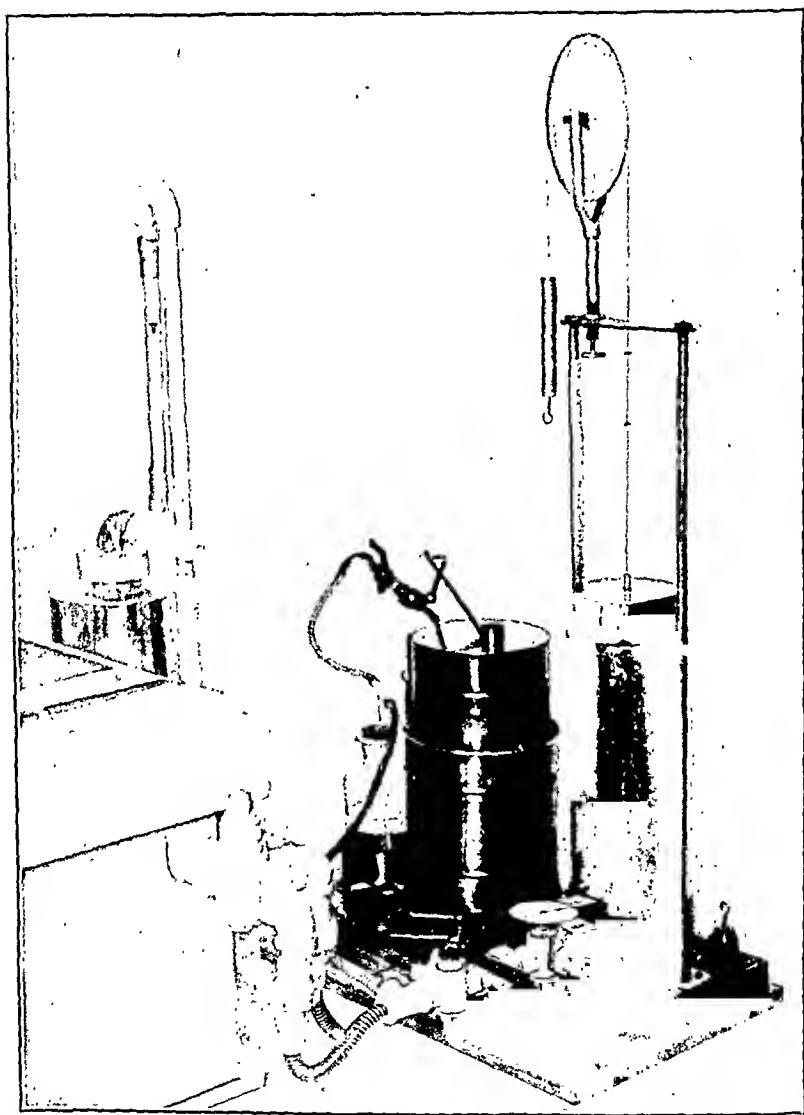


Fig. 3.—Densimometer and gas regulator of respiration apparatus for continuous administration of helium-oxygen mixture to infants.

the chamber will be completely swept out and the system will be filled with the desired mixture. By shutting valve *H* during the early part of the filling and by opening valve *Q* to connect with regulator *E* and valves *M* and *L* to connect with spirometer *K*, the reservoirs of the units *E* and *K* can by manual manipulation be washed out with the oxygen-helium mixture and then partially filled with this mixture. This is done to prevent the introduction into the system of gases other than the desired mixture. This extra gas replaces gas used in testing the composition of the mixture.

*Method of Analysis of Gaseous Content of Chamber.*—It is important to know that the gaseous mixture inside the chamber is composed of the desired percentages of helium and oxygen and that this composition remains constant during the use of the equipment. It is also necessary to know that the infant has sufficient oxygen at all times. Therefore a simple method for determining the composition of the gaseous mixture was needed. For this purpose a densimometer (Fig. 3 and *K*, Fig. 2) was designed, based upon the principle that, because of the difference in density of helium and oxygen, the rate of effusion of a mixture of these gases will vary according to the composition of the mixture. The densimometer consists of a 1-liter spirometer, the bell of which (originally exactly counterpoised) is overweighted by a 100 gm. brass ring. The spirometer is sealed with mineral oil.\* Provision is made for passage of the gas from the spirometer through an orifice in the disk *N*. This disk (enlargement *P*, Fig. 2) is of brass, 0.8 mm. thick, in which an orifice 0.23 mm. in diameter has been made with a No. 80 drill. Even with great care the size of the orifice produced by the No. 80 drill will not be uniform in all cases. A number of disks with these orifices were made and tested. After a standard time for passage of a given quantity of gas had been established, the orifices of the disks that required longer than the standard time for the passage of gas were enlarged by reaming with a needle. Disks with orifices permitting too

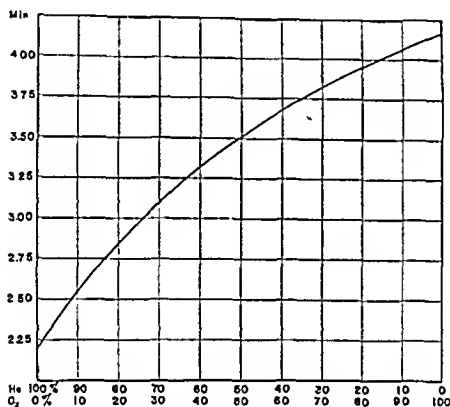


Fig. 4.—Calibration curve obtained with densimometer. The curve shows the time in minutes required for a definite volume of a gaseous mixture, having the composition indicated by the abscissae in the chart, to escape from the closed system through the standard orifice.

rapid flow of gas were discarded. After the air originally in the densimometer has been swept out, the instrument is filled with the gaseous mixture, the composition of which is to be determined. This is accomplished by connecting the densimometer with the ventilation system, closing valve *H*, and manually raising the bell of the densimometer. The gas thus withdrawn from the system into the densimometer is replaced by gas from regulator *E*. The gas in the spirometer bell is washed back into the system, and the bell is then filled again, to secure as representative a sample as possible. The test of the gas is then performed by turning valve *L* to the position shown in Fig. 2 and noting the time required for a portion of the gas in the spirometer *K*, under the pressure caused by the 100 gm. excess weight of the bell, to pass through the orifice at *N*. Two marks 50 mm. apart on the counterpoise cord (Fig. 3) designate the volume to be measured. The time required for these two marks to pass a fixed point is a measure of the rate of effusion of the gaseous mixture. From the results of calibration tests of the densimometer with ordinary air, pure oxygen, pure helium, and various helium-oxygen mixtures, the calibration curve in Fig. 4 has been derived. This curve indicates the percentages of oxygen and helium in the gaseous mixture in the system, according to the established rate of effusion from the densimometer. The practicability of this instrument is demonstrated by the fact that a second densimometer was constructed and adjusted to

\*Squibb's heavy California mineral oil.

have the same calibration curve for standard orifices. If dust or other foreign material clogs the orifice, it is best to replace the disk by another tested disk rather than to attempt to clean the orifice. For convenience, several disks are kept at hand in a sealed container. To control the accuracy of functioning of the instrument and to make sure that the orifice is clean, the time for diffusion of room air ( $3.98 \pm 0.04$  minutes) is used as a standard.

*Automatic Replacement of Oxygen.*—To maintain constancy in the composition of the gaseous mixture when the infant is in the chamber, the oxygen consumed by the infant is constantly replaced by an automatic arrangement connected at *Q* (Fig. 2). This consists of a Murrill regulator,<sup>3</sup> which has its bell floated by a cork ring attached at *o, o*. As the volume of the gaseous mixture in the closed system is decreased by the infant's consumption of oxygen (the carbon dioxide produced by the infant is removed by the soda-lime), the tendency for reduced pressure in the system causes replacement of the oxygen from container *E*. As the bell of this instrument falls, it causes valve *G* to be opened, admitting oxygen from the supply line. By a tee dipping into the bottle *F*, containing water, oxygen from a cylinder is constantly supplied under approximately 25 mm. of water pressure to the valve *G*, at a rate of 30 to 50 c.c. per minute. As the bell is raised by the admittance of oxygen, the valve *G* closes and the excess oxygen escapes through bottle *F*. But if valve *G* is open, oxygen will be supplied to the container *E* without contamination, any excess oxygen escaping into the room. As the chamber, with its blower and connecting pipes, has a total capacity of 40 liters, it would contain 10 liters of oxygen when a 25 per cent oxygen mixture is used. If for any reason oxygen failed to be supplied, the chamber would continue to have sufficient oxygen for the infant's needs for at least two hours (the rate of oxygen consumption of these infants has been found to be approximately 20 c.c. per minute) without the oxygen percentage being reduced to an unphysiologic level.

*Use of Other Percentage Mixtures of Helium and Oxygen or of Mixtures of Other Gases.*—Some infants have benefited by the gas mixtures of low density, but others have required higher oxygen concentration to improve their condition. The oxygen content of the chamber air can be readily increased by admitting oxygen through the valve *V* (Fig. 2) until a calculated quantity of gas in the chamber has been displaced. This is done by stopping the blower, turning valve *V* so that it does not communicate with blower *B* but does communicate with the pipe *A* and the oxygen supply. This insures that the oxygen introduced will go into the chamber. The volume of gas introduced is determined by metering the gas displaced, by connecting to the valve *M* an ordinary wet gas meter or spirometer. If, for example, a mixture of 40 per cent oxygen is desired and the gas already present in the chamber contains 25 per cent oxygen, by displacement of 7 liters of the contents with pure oxygen the oxygen percentage will be increased to approximately 40 per cent. The composition of the new mixture can be readily tested, to insure that the desired percentage of oxygen has been attained. This new percentage will then be automatically maintained, as the oxygen used by the infant will be replaced by the automatic arrangement. In some cases it is desirable to use a mixture of carbon dioxide and oxygen as a respiratory stimulant. This mixture can be admitted in the same manner as described above for enrichment of the oxygen content of the chamber air. When the carbon-dioxide and oxygen mixture is used in the chamber, the ventilation system must not be in operation, as the soda-lime would remove the carbon dioxide. When it is desired to resume the use of the chamber with some other gaseous mixture, the mixture of carbon dioxide and oxygen should be swept out into the room and not through the ventilation system, as otherwise the carbon-dioxide absorption capacity of the soda-lime will be exhausted unnecessarily soon and the technical problem will be encountered of compensating rapidly for the decrease in volume of the gas in the system.

*Test for Tightness.*—The apparatus is readily tested for tightness by closing valve *Q* to the system, having valves *M* and *L* open to the spirometer, and valves *S* and *V* in the position shown in Fig. 2. The bell of spirometer *K* (which has been overweighted by 100 gm. for use as a densimeter, see page 65) is exactly counter-

balanced by attaching a 100 gm. weight to the counterpoise cord; the level of the bell is then noted, and the weight is removed. This places slight pressure on the system, because of the original overweighting of the bell. After fifteen or twenty minutes the weight is replaced, and if the system is tight, the bell should return to its original level. Slight changes in temperature and slight changes in pressure on the chamber, caused, for example, by placing something on the cover, will alter the apparent volume of the system.

#### ACTUAL USE OF INCUBATOR

In actual use this incubator has proved excellent in providing the essential conditions for infants needing special care. The temperature is adequately maintained and, even when the chamber is open, the chamber walls prevent marked exposure of the infant to cold. The humidity is maintained in the vicinity of 90 per cent by the use of Wilson soda-lime. Our experience with this incubator has been confined to infants of diabetic mothers. These infants have required attention usually every four hours, to obtain blood samples for sugar determination and for other care. Over a period of four hours, with the chamber sealed, the composition of the gas has been held essentially constant in all cases. The infant is visible through the large window (which could be even larger, if desired) and is readily accessible in the event that immediate attention is needed. It is frequently helpful to have little or no covering on the infant, to facilitate observation and to avoid any possible hindrance to respiration. In this case, the temperature can be held at such a level that the infant will require little or no covering.

Between May, 1936, and May, 1939, ten infants of diabetic mothers were placed in the oxygen-helium incubator in an attempt to combat neonatal asphyxia. The clinical picture associated with fatal asphyxia neonatorum in our experience had been slight respiratory excursion, rising temperature, long periods of apnea and cyanosis, and the development of terminal rales. For many years this picture had been attributed to hypoglycemia due to maternal insulin or hyperplastic islet tissue. The latter is an almost universal finding at autopsy. Our own belief, however, was that hypoglycemia could not be the responsible factor, as it occurs in normal infants without abnormal behavior, is remedied easily by glucose, and the seizures observed in our children were found to occur with blood sugar values above normal and at normal levels as well as below normal. Eventually, through the work on hormones by Smith and Smith<sup>4</sup> and later the prolactin determinations by White and Hunt,<sup>5</sup> it became apparent that the fatalities could be predicted by a knowledge of the prolactin balance and prevented by substitutional estrin and progesterone therapy. Thus, among the infants of 14 mothers whose values for prolactin were maintained at a normal level by treatment with massive doses of estrin and progesterone three to six weeks prior to delivery, there were 2 deaths, 1 neonatal associated with asphyxia pallida in a premature infant and 1 stillbirth. In the latter instance, the mother's therapy had been omitted. Among the infants of twelve mothers with supernormal values for prolactin, there were 6 fatalities, 4 associated with prematurity and asphyxia and 2 stillbirths.

Ten infants were placed in the incubator, all of whom had respiratory difficulties or were cyanotic. The mothers of 6 of these had supernormal values for prolactin and their infants were, therefore, in the group in which the mortality rate was high. Despite the oxygen-helium treatment, 3 of these infants died. Hence this treatment does not always result in a successful outcome in this particular complication. Of the 4 infants whose mothers had normal values for prolactin, all survived, but we know now that this was to be expected in nearly 100 per cent of these cases. One infant, we believe, was distinctly helped. This infant, who had aspirated amniotic content and for whom the pediatrician had given a fatal prognosis, had long periods of cyanosis without periods of apnea. The cyanosis was relieved when the infant was placed in an atmosphere of almost pure oxygen. She remained in the incubator for forty-eight hours, and then behavior became entirely normal. Two other infants also survived, being apparently aided to some extent by the oxygen-helium treatment. Although this treatment was not successful in all instances in preventing respiratory

failure, in general the infants were less cyanotic and respiration was better when they were in the controlled atmosphere of the incubator.

### SUMMARY

An incubator is described in which an infant can be kept at the proper temperature and humidity, with proper ventilation and, to facilitate respiration, in an atmosphere containing a known and controlled mixture of oxygen and helium. A densimometer serves to determine the composition of the gaseous mixture within the chamber and to make certain that this composition remains constant during its use. When necessary, a mixture of carbon dioxide and oxygen can be used as a respiratory stimulant. Originally the incubator was designed for newborn infants of diabetic mothers, in an attempt to combat neonatal asphyxia, and the equipment has proved helpful in several instances. Subsequently it was found that the respiratory failure of such infants can be successfully prevented by prenatal hormone therapy. The clinical experience with the incubator is discussed.

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## LEUCEMIC INFILTRATION OF THE FEMALE INTERNAL GENITALIA AS A CAUSE OF VAGINAL BLEEDING

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THE leucemias have always constituted a sphere of medicine into which the gynecologist rarely, if ever, entered. The patient suffering with leucemia would come to the surgeon because of enlarged lymph nodes, to the internist because of an enlarged spleen, or to the dermatologist because of infiltrations of the skin. In the case reported in this paper, the leucemic patient came to the gynecologist because of vaginal bleeding, and the constitutional disease was discovered by investigation of the cause of the bleeding. Since women are being educated to the importance of ascertaining the cause of any abnormal vaginal bleeding, some cases of leucemia may be discovered and diagnosed by the gynecologist.

Leucemic infiltration of the female genitalia has always been a rare entity, although it may have been present in some cases where it was either undiscovered or not diagnosed.

The textbooks and handbooks in gynecology (with one exception) make no mention of a relationship between leucemia and pelvic pathology. MacCallum refers to a case of a lymphoid nodule in the cervix uteri extending to the vagina, with ulceration and bleeding. At autopsy there was found "an infiltration of lymphoid cells in many of the organs in association with a leucemic condition of the blood." Leucemic infiltration may occur in any part of the body, although, as noted by

Ewing<sup>1</sup> and Stout,<sup>2</sup> infiltration of the genitalia is the rarer form. Rusch<sup>3</sup> in 1914, reported a case of leucemic infiltration of the labium minus and also referred to a case of Herz (Zit. bei Arzt und Fuhs) in which there was a similar infiltration in the posterior commissure of the vagina. Kulka<sup>4</sup> in 1932, reported a case of lymphatic leucemia in which the infiltration of the clitoris assumed such a form that it was mistaken for a carcinoma.

As for the infiltration of the internal genitalia, Schlagenhauser<sup>5</sup> seems to have been one of the earlier authors to describe it. In his case the patient had uterine bleeding besides bleeding both subcutaneous and from the gums. This was a case of lymphatic leucemia, and examination of the entire uterus, the ovaries and parametria at necropsy revealed a leucemic infiltration in all of them, besides a chloroma of the fundus of the uterus. Thaler<sup>6</sup> reported an autopsy in a case of acute leucemia in a young woman who had tonsillar abscesses and profuse vaginal bleeding (uncontrollable). Histologic examination showed a leucemic infiltration of the tubes; the uterus and ovaries were uninvolved. The infiltration was described as being composed of lymphoid and myeloid elements (the latter elements may have been due to the fact that there was a purulent salpingitis, bacteriologically identical with the throat culture).

Geipel<sup>7</sup> in 1920, presented the necropsy findings in two cases of lymphatic leucemia. In one case there was a heavy lymphocytic infiltration of the uterus, tubes, and ovaries (the endometrium being the least involved). In the other case, the infiltrate was present only in the deeper layers of the endometrium (the tubes and ovaries were not examined). In both cases there was an atrophy of the endometrium, and the cervix showed a minimal infiltration, and this, for the most part, perivascular.

Brakemann<sup>8</sup> also reported an autopsy of an acute leucemic patient in whom the ovaries, tubes, entire uterus, and vagina were involved with the infiltration. Parenthetically, we might mention that he was the only one to intimate a relationship between the vaginal bleeding and the leucemic infiltration. He stated that irregular profuse vaginal bleeding associated with bleeding from other bodily orifices should suggest leucemic involvement of the genital organs.

Poynder<sup>9</sup> reported a case of chloroma of the uterus discovered at autopsy. This patient had had severe metrorrhagia for several months before death. A diagnosis of acute myelogenous leucemia was made from the findings at autopsy, although there had been no blood count done before death. This case and that of Schlagenhauser are the only ones in which the infiltration was made evident by this greenish tumor in addition to the usual infiltration.

Neumann<sup>10</sup> referred to a patient with myelogenous leucemia whom he had curetted twice, but in whom he had found no infiltration. He also referred to necropsies in cases of myelogenous leucemia reported by Laubenberg, Geipel, and Bower and Clark, in which there was no infiltration of the genital organs.

In 1934 Pietro<sup>11</sup> reported the autopsy findings in a case of leucemia where he found that the leucemic infiltration had involved, among other organs, the cervix and right ostium of the Fallopian tube. The cervix was so heavily involved that there appeared to be a tumor in it on gross examination.

Held and Kieve<sup>12</sup> reported a case of acute myelogenous leucemia with retrobulbar and cervical tumors. Autopsy revealed a round cell infiltration of numerous organs including the cervix, causing a "tumor" of the latter. Since the white blood cell count was 8,800 with a hemogram showing 19 per cent monocytes, it seems that this case might fall more readily into the category of a lymphosarcoma rather than into that of a myelogenous leucemia.

Villata<sup>13</sup> performed autopsies on two cases of lymphatic leucemia; and on histologic examination of the uterine wall he found lymphocytic infiltration of all three layers.

Novak<sup>14</sup> discussed the occurrence of abnormal vaginal bleeding in cases of leucemia. He quoted Virchow as to the frequent association of menstrual disorders with leucemia. Menorrhagia and metrorrhagia occurred more commonly than deficient menstruation. He also noted that Mosler found in 21 cases of leucemia 16



which showed some form of menstrual anomaly. In many, menstruation was entirely absent and in only 2 of the cases was there any profuse menstruation present.

Kahn<sup>15</sup> reported a case of a patient, aged 45 years, with acute leucemia who had had regular menses until two weeks before admission to the hospital. At that time she began having profuse uterine bleeding which persisted until, and was the cause of, her death in spite of all attempts to stop the bleeding. Nothing abnormal was found on pelvic examination and no autopsy was done.

McDonald and Waugh<sup>16</sup> on July 26, 1939 reported a case of leucemic infiltration of the endometrium, found in a living woman.

The case report which follows is that of a woman who complained of vaginal bleeding, and investigation of the pelvis led to a diagnosis of lymphatic leucemia through biopsies of the endometrium and of the cervix.

A white widow, aged 67, complaining of vaginal bleeding of one year's duration, as well as weakness and fatigability during the same period, presented herself for the first time on Feb. 20, 1939. The family history was irrelevant, except that the patient's husband died of pulmonary tuberculosis twenty-five years ago.

The patient had typhoid fever at twenty-two years of age. Three years ago she had a squamous cell carcinoma of the urethral meatus treated with radium. Two years ago she had a recurrence approximately 1.5 cm. within the urethral canal, which was successfully treated with radium, and she has had no recurrence since then. Questioning as to systemic history revealed that the patient was troubled with frequent colds, cough, and dyspnea upon moderate exertion, as well as arthritis of her hands and knees.

She had two pregnancies. One of these terminated in a normal full-term infant; the other in a spontaneous abortion at four months.

The catamenia began at the age of nineteen or twenty years and occurred regularly every month. Each period lasted three or four days. The menopause occurred twenty-five years ago.

From the time of her menopause, twenty-five years ago, the patient did not have any vaginal discharge or bleeding until the onset of the present illness. During the previous year she had had vaginal discharge of red blood without any clots, necessitating the use of two sanitary napkins during the day and one napkin through the night.

#### PHYSICAL EXAMINATION

The patient was an obese woman with a pallor of the skin, but not a corresponding pallor of the mucous membranes. The pertinent positive physical findings were: Bilateral submaxillary glands palpable, enlarged, firm, freely movable; blood pressure 180/110; the heart was enlarged slightly to the left by percussion. The spleen was enlarged to 3 cm. below the costal margin; there was a reducible left inguinal hernia. There was a moderate amount of bleeding from within the vagina upon examination. A small cyst was present at the posterior fourchette. The vaginal mucosa was fairly smooth except for the left portion of the anterior fornix and the entire posterior fornix. Numerous discrete, small nodules, each about the size of a pinhead, could be felt in the mucosa in these areas. The cervix was enlarged to about three times the normal size in a patient this age (approximately 5 cm. by 3 cm.) by a soft, irregular tumor (almost the consistency of a cervix in a pregnant patient). Examination of the uterus revealed nothing abnormal, and it was freely movable. No abnormal masses or tenderness were found in the adnexal regions. By speculum examination, the cervix was found enlarged, as described above, with free bleeding coming from it. The color, consistency, and appearance could best be compared to that of the cortex of a kidney. A biopsy was taken of the endometrium with a suction curette and a biopsy was also taken of the cervix.

*Laboratory Data.*—Urine: Albumin + with many red blood cells and white blood cells on microscopic examination of the sediment. Examination of a voided specimen after cessation of bleeding showed a trace of albumin with many white blood cells present on microscopic examination.

April 8, 1939. Platelet count—202,100/c.mm.

Bleeding time = 1 minute. Clotting time =  $3\frac{3}{4}$  minutes.

Basal metabolic rate + 11 per cent. Kahn—negative.

BLOOD COUNTS:	R.B.C.	W.B.C.	STAB	SEGS	JUV.	EOS.	BAS. LYMPH.	MONO.
4/ 5/39	5,000,000	33,350	0	20	0	1	1	70
4/11/39	4,700,000	35,000	0	20	0	1	0	75
4/24/39		27,700	0	22	0	0	1	74
4/26/39		26,250	1	22	1	0	0	73
4/28/39		17,900						
5/ 1/39		28,800						
5/11/39		12,750	1	42	0	1	0	47
5/22/39		14,200	1	44	0	3	0	46

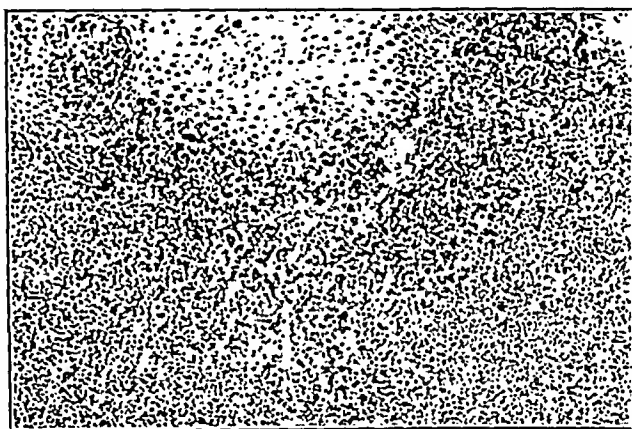


Fig. 1.—Cervix showing infiltrated stroma and overlying epithelium.  $\times 140$ .

*Roentgenograms.*—*Chest:* There was some suggestion of increased width in the right hilar area of the mediastinum. There was cardiopneumosis of the heart shadow and increased dimensions, particularly toward the left side. *Knees:* There were marked hypertrophic osteoarthritic changes; and, in addition, the joint cartilage of the right knee showed almost complete absorption and partial ankylosis. *Hands:* The phalangeal joints of both hands showed marked hypertrophic bone lipping and the distal joint cartilage showed marked absorption changes. *Abdomen:* There was a splenic enlargement, and the spine and pelvic margins showed hypertrophic bone changes.

On April 19, 1939, a dilatation and curettage of the uterus was done. The cavity and cervical canal measured  $2\frac{1}{2}$  inches. Curettage of the uterine cavity showed it to be regular, and a very scant amount of curettings were obtained. There were no polyps or irregularities felt with the curette. The small cyst at the fourchette was excised for biopsy.

On April 22, 1939, deep roentgen ray therapy was begun over the area of the spleen with a 200 K.V. machine. Five treatments of 100 r. each (measured at the skin) were given approximately every other day. The portal used was 10 cm. by 10 cm. with a filter consisting of  $\frac{3}{4}$  mm. Cu at a target skin distance of 50 cm. A constant check was made of the blood count during this therapy. After several treatments had been administered all the vaginal bleeding ceased.

On May 11, 1939, examination showed the spleen to be much smaller, the tip being just palpable at the costal margin. The cervix had decreased in size, being approximately 3 cm. by 2 cm., and the nodulations in the vaginal mucosa in the fornices had entirely disappeared.

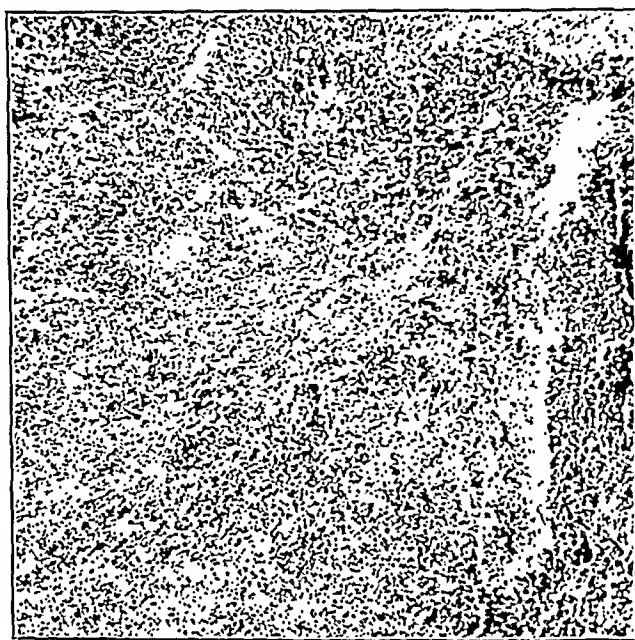


Fig. 2.—Shred of tissue obtained upon curetting uterine cavity.  $\times 140$ .



Fig. 3.—Cervix showing stroma and small areas of infiltration remaining after therapy.  $\times 140$ .

#### HISTOPATHOLOGY

Examination of the tissue from the cervix (Fig. 1) showed a heavy round cell infiltration of the entire fibromuscular stroma of the cervix. This infiltration did not involve the cervical glands or the overlying epithelium. It was found to be the lymphocytic cell (large and small) infiltration which composes leucemic infiltrates.

In some sections there were areas of stroma free of the infiltration. This infiltration should not be interpreted as an infiltration of acute or chronic inflammation or of granuloma.

In the small shred of tissue obtained upon curetting the uterine cavity, the same infiltration of the stroma (Fig. 2) was found as was present in the cervix. The absence of endometrial glands in this shred of tissue was not unexpected, since this was a senile endometrium.

In Fig. 3 is represented the cervical fibromuscular stroma after the completion of, and response to, therapy. The stroma could be readily seen with the round cell infiltration occurring in areas here and there.

The cyst removed from the fourchette proved to be a sebaceous cyst.

#### DISCUSSION

As may be noted in the discussion of the literature in the earlier part of this paper, all the cases of leucemic infiltration of the internal genitalia were those found at autopsy. Never before had a case of this sort been reported in a living woman until the one reported in July, 1939, by McDonald and Waugh.<sup>16</sup>

Not any less interesting than the diagnosis of leucemic infiltration of the genitalia in a living woman is the fact that the examination of the tissue removed by biopsy led to the diagnosis of her constitutional disease of leukemia. When the tissue, removed by biopsy, was examined under the microscope, the impression was that the lymphocytic infiltrate was probably due to a leukemia. Blood counts, hemograms, and the splenomegaly corroborated this impression. (The hemograms were studied in the fixed stained smear as well as with the supravital stains.)

Since the involvement is present in the vagina, cervix, and endometrium, it would be logical to assume that the myometrium is also involved.

Kahn<sup>15</sup> reviewed 8 cases of leukemia in female patients in the hospital records. In 6 of them the menstruation was undisturbed, but in the other 2 the menstrual bleeding was excessive, prolonged, and occurred with increased frequency. The question arises whether in these two cases of leukemia there might not have been an infiltration of the internal genitalia as a cause for the abnormal vaginal bleeding.

In this case the involvement could be studied as well as the beneficial effect of the therapy. The excellent response to the irradiation over the spleen is manifested by the diminution in the blood count and improvement in the hemogram, as well as by the disappearance of the bleeding and of the nodular infiltration of the vagina and by the reduction in the size of the cervix.

Brakemann<sup>8</sup> was the only author who intimated a possible relationship between the leucemic infiltration of the genitalia and the vaginal bleeding, while McDonald and Waugh<sup>16</sup> state that there is a definite relationship. We believe there is a direct relationship as proved by the disappearance of the bleeding after the therapy was instituted. There is nothing else to account for the vaginal bleeding as far as any disturbance in the clotting mechanism of the blood, adnexal tumors, polyps, or vaginitis is concerned. The platelet count and bleeding and

clotting time were all found to be normal. The cessation of bleeding after irradiation over the spleen would contradict any claim for any of these as the etiologic agent as well as any consideration of a hormonal basis.

One other case has come under our observation in which a cervical polyp was removed, and upon routine histopathologic examination a lymphoid cell infiltration was found in it, as well as in several areas of the fibromuscular stroma of the cervix. At the time, the blood picture was quite suspicious, but at a later date a study of the bone marrow could not corroborate it as a proved case.

Since the age incidence of leukemia corresponds fairly well to that of the menopause, it does not seem too far fetched that other cases of leukemia may be discovered when patients come to the gynecologist because of abnormal vaginal bleeding (either just before or after the menopause). Any competent gynecologist confronted with a problem like this would remove tissue for histologic study (cervical, if the cervix were involved, and endometrial). Then examination of the tissue may lead to the possible diagnosis of a leukemia instead of an "empirical" diagnosis of menopausal bleeding or of endocrine disturbance. One of the most likely mistakes is that the tissue removed for microscopic examination may be diagnosed as chronic endocervicitis or chronic endometritis on cursory examination. The cases of early involvement may show a minimal amount of infiltration; or else a section may be obtained which would show infiltration in one portion and not in another. However, this is not so likely to disconcert the pathologist when the entire section is carefully examined.

All the cases of this infiltration of the genitalia are reported from foreign countries and none (except for the case of McDonald and Waugh) have ever been reported from this country. Yet there is no geographic distribution of the disease. A logical deduction would be that there are probably quite a few cases in which the genital infiltration is never discovered. It seems to be a possibility that there may be an infiltration localized to the uterine wall, as described in Villata's<sup>13</sup> cases, and thus the cervix would fail to show any abnormality. The cause for the bleeding in a case like this would be obscure and careful examination of the tissue removed by curettage could lead to the diagnosis. (These latter lines of assumption were written before the publication of the case of McDonald and Waugh and are proved by that case.)

#### SUMMARY

This is a case of chronic lymphatic leukemia. The leucemic infiltration of the endometrium, cervix, and fornices of the vagina is discovered for the first time in a living woman. Furthermore, the examination of the tissue removed by biopsy led to the diagnosis of the disease. The relationship between the infiltration and abnormal vaginal bleeding is discussed. The beneficial response to therapy is demonstrated.

The authors wish to express their appreciation for the cooperation of Drs. Carl V. Moore and Harry Agress in the hematologic studies.

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## VAGINAL ACIDITY (IN VIVO GLASS ELECTRODE MEASUREMENTS) IN LATE PREGNANCY AND ITS RELATION TO THE VAGINAL FLORA

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A PREVIOUS communication from this department<sup>1</sup> detailed a method for determining the pH of the undiluted vaginal discharge by a quinhydrone microelectrode. It was shown that the acidity varied with the character of the vaginal flora and was higher as the number of the vaginal bacilli of Döderlein increased. In general, the pH was slightly higher in pregnant than in nonpregnant women, and somewhat lower in the upper than in the lower vagina. The available literature up to 1936 was also reviewed.

The recent development of glass electrodes of a high degree of accuracy and in a multitude of designs has stimulated a repetition of this work in connection with certain investigations upon the flora of the vaginas of normal pregnant women in the last weeks of gestation. The glass electrode technique possesses the great advantage of permitting rapid and accurate determinations in vivo at any designated level in the vagina.

### MATERIAL

Two hundred ante-partum women admitted to the University Hospital for delivery and post-partum care were subjected to glass electrode pH determinations on the vaginal discharge. In addition, studies were made of (a) gram-stained spreads of the discharge, and (b) cultures for the Döderlein bacilli, for monilia, and for the *Trichomonas vaginalis*, according to the following techniques.

### TECHNIQUES

*Glass Electrode Hydrogen-Ion Determinations.*—The Cameron pH-meter (Fig. 1) consists of a "detector unit" (containing an amplifying tube and carrying a saturated calomel electrode and a glass electrode), a potentiometer calibrated directly in terms of pH, and a ten-foot connecting cable to permit convenient operation. With the patient in the lithotomy position, the detector unit is held close to the vulva, the glass electrode is inserted into the vagina to the desired depth, and the

circuit is completed by placing in the vagina beside the electrode a sturdy blunt-tipped capillary tube which is connected with the potassium-chloride reservoir of the calomel electrode by a rubber tube filled with saturated potassium chloride. The difference in potential between the two electrodes depends upon the pH of the vaginal discharge and is indicated as such on the potentiometer. The procedure, which can be completed in a few seconds, rarely causes any discomfort, and permits rapid readings at several levels.

The glass electrodes are readily cleansed between tests with soap and water and alcohol. When not in use they should be kept in water. The potassium-chloride junctions are not so easily cleansed and it is advisable to have several available in order to conserve time. After use they are immersed for ten minutes in 2 per cent phenol solution, washed with soap and water, and rinsed with distilled water under pressure. Before they are used again they are filled with saturated KCl solution from the reservoir, care being taken to exclude all bubbles.

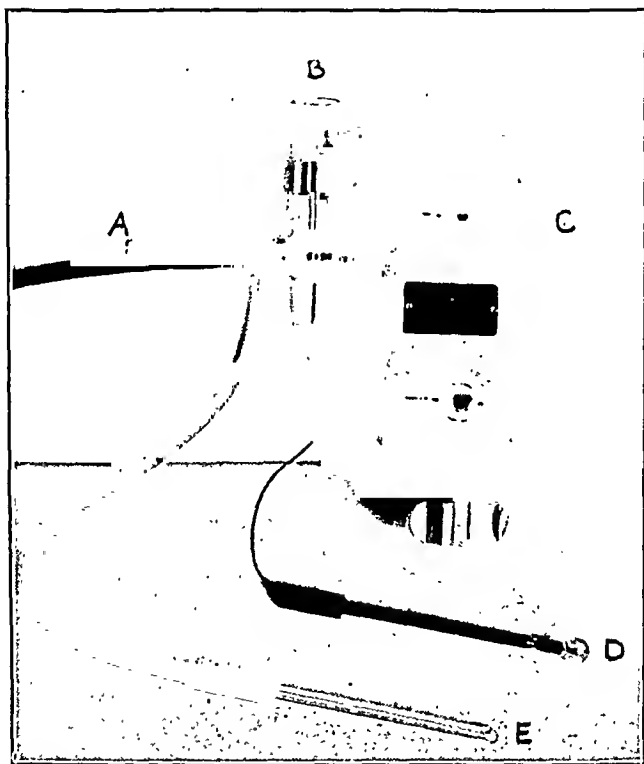


Fig. 1.—The Cameron pH meter. A, Cable to potentiometer; B, calomel electrode; C, detector unit; D, glass electrode; E, potassium chloride junction.

The difference in temperature between the glass electrode (vaginal temperature) and the calomel electrode (room temperature) disturbs the potentiometer readings so slightly (one-half times 0.015 pH per 5° C. temperature difference times the pH unit difference between the point of calibration, pH 4.0, and the test level, 3.96 to 6.99) that the corrections have not been introduced.

Early in the study certain difficulties were experienced in obtaining constant readings because of one or more of the following factors: (1) Faulty glass electrodes due to "bubble etching," an error which can be eliminated by standardizing the electrodes with a known buffer of pH 4.0 and checking them against a buffer solution of pH 7.38. (2) Contact of the glass electrode with the cervix which exposes it to both an alkaline (the cervix) and an acid (the vaginal wall) environment, thus making constant readings impossible. Pulling the electrode away from the cervix obviates this difficulty. (3) Failure to complete the circuit, so that no read-

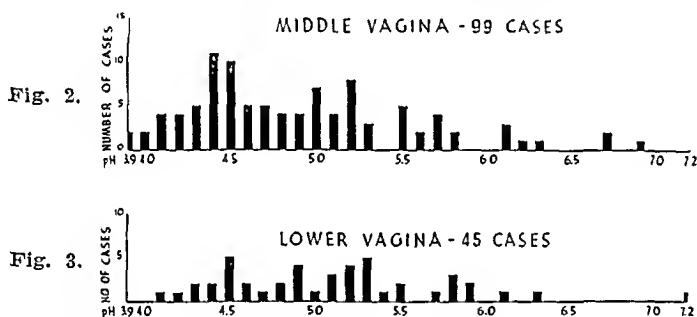
ing can be obtained. Rotation of the glass electrode and of the KCl junction tube, and occasionally flushing a small amount of the KCl solution through the tube will usually restore normal operating conditions promptly.

### BACTERIOLOGIC STUDIES

Consistent attempts were made to take the material for spreads and cultures from the portion of the vaginal wall contacted by the tip of the glass electrode. For the lower vagina, the labia were separated widely and the discharge collected from the area immediately inside the closed portion; while a sterile Graves' speculum was employed to expose the higher portions of the canal. Three swabs were inoculated from each patient and were treated as follows:

Swab 1 was spread directly on a clean glass slide, and then dropped into a tube of 5 per cent human serum in Ringer's solution over a placenta infusion agar slant. The original spread was stained by the Hucker modification of the Gram technique and examined under the oil-immersion lens. The flora was classified according to Schroder.<sup>1</sup> The culture was incubated at 37° C. for eighteen to twenty-four hours, when the sediment was examined for motile trichomonads.

Swab 2 was placed in a tube of 1 per cent lactose broth and incubated in a McIntosh-Fildes anaerobic jar for forty-eight hours. One drop of this culture was then stained and examined for gram-positive rods, while a second drop was inoculated onto the surface of a Difco tomato agar plate, which was incubated in an



Figs. 2 and 3.—Glass electrode measurements of acidity in the middle and lower vagina.

atmosphere containing 10 per cent carbon dioxide for forty-eight hours, and then examined under the low-power lens. If the colony development was not typical, the growth was transferred to a slide and stained with the Gram technique. The presence of discrete colonies with yellowish centers or translucent colonies with filamentous offshoots and the demonstration of typical gram-positive rods were assumed to indicate the presence of the vaginal bacilli of Döderlein.

Swab 3 was rubbed over the surface of a Sabouraud's agar slant and then used to inoculate a tube of Sabouraud's broth. After forty-eight hours, visible growths were transferred to a slide and stained by the Gram technique. The presence of large gram-positive ovoid cells and budding conidia was assumed to show the presence of "monilia." The fungus was then isolated in pure culture and stored for future study of mycelium and ascospore production (the "monilia" produce the former but not the latter).

### RESULTS

*Vaginal pH.*—The pH readings agreed closely with those previously reported<sup>1</sup> for pregnant women, and confirmed the earlier observation that the discharge in the lower vagina is usually less acid than that obtained from the middle portion of the canal, especially when the discharge is scanty and does not flow readily. The distribution of the pH values in the middle vagina is indicated in Fig. 2 and that in the lower vagina in Fig. 3.



TABLE I. INDIVIDUAL DIFFERENCES IN pH OF THE MIDDLE AND LOWER VAGINA

PATIENT	LOWER VAGINA pH	MIDDLE VAGINA pH	DIFFERENCE IN pH
61	6.30	5.29	1.01
62	7.20	6.88	0.32
163	5.96	5.84	0.12
165	4.20	4.09	0.11

Table I shows typical differences obtained in individual patients.

*Relation Between pH and Vaginal Flora.*—The relation between the vaginal acidity and the flora as observed in the stained discharge is shown in Table II.

TABLE II. RELATION BETWEEN pH AND VAGINAL FLORA

(Based Upon 140 Satisfactory pH Measurements)

TYPE OF FLORA (SCHRODER)	HYDROGEN-ION CONCENTRATION					
	MIDDLE VAGINA			LOWER VAGINA		
	CASES	AVERAGE	RANGE	CASES	AVERAGE	RANGE
I	46	4.58	3.96-5.72	14	5.13	4.43-6.30
II	31	5.03	3.99-6.10	25	5.13	4.16-5.98
III	17	5.69	4.92-6.88	7	5.54	4.58-7.20

The bacterial flora observed in spreads from the lower vagina (just inside the introitus) frequently does not agree with the Schroder type expected on the basis of the measured pH. Individual cases brought out this fact more strikingly than do the average values presented in the table, and suggest that some factors other than pH have a role in the control of the bacterial growth near the introitus.

*Döderlein Bacilli Cultures.*—Among the 195 cultures for Döderlein bacilli (5 patients were not cultured for this organism) in lactose broth, 185 contained gram-positive rods morphologically similar to the vaginal bacilli. On the tomato-agar subculture plates, there were 173 positive cultures and four plates were overgrown by bacterial "spreaders" or molds. Eight of the subcultures did not substantiate the findings in the original cultures, and it is uncertain whether the bacilli observed in the spreads were of the Döderlein group or whether the failure to recover them was due to insufficient anaerobic cultivation.

Among the 200 spreads examined during classification of the discharges, 29 showed no gram-positive rods (Type III). However, gram-positive bacilli were grown in 24 of the 29 original broth cultures from patients with Type III discharges, and in 18 instances the bacilli were identified as Döderlein bacilli in the tomato-agar subcultures. Obviously the absence of gram-positive rods in spreads does not justify the conclusion that there are no Döderlein bacilli in the discharge, but for practical clinical purposes the stained spread offers a convenient index to the character of the vaginal flora.

*Monilia Cultures.*—Yeast-like fungi were obtained from 68 patients (34 per cent), a figure considerably higher than that (22.4 per cent) recorded in a previous study of cultures from the cervix and posterior fornix,<sup>2</sup> and more than three times that noted in the recent communication of Waters and Cartwright.<sup>3</sup> The majority of the cultures in the present series were obtained from the midportion of the vagina where the pH is somewhat lower than in the cervical region. The use of both Sabouraud's broth and Sabouraud's agar slants slightly increased the number of positive cultures: In 8 instances the slants were positive and the broth negative, whereas in 9 cases the reverse was true.

Satisfactory pH readings were obtained from 30 of the 68 patients who harbored monilia. The range of acidity was from pH 3.96 to pH 6.99, with an average of pH 4.96. Twenty-four of these 30 patients presented Type I or II discharges.

Among the 6 with Type III flora, the pH readings were 4.92, 5.27, 5.28, 5.71, 6.11, and 6.99, respectively, and the growth was relatively sparse on both culture media. The heaviest growth of fungi occurred with the more acid discharges. In 6 of the 9 cases where the organism grew only in the broth medium, the pH range was 3.99 to 6.99, and the average was 5.37.

*Trichomonas Vaginalis*.—Twenty-three (12.1 per cent) of the 190 trichomonas cultures were positive. This is in sharp contrast to the findings in material taken from the upper vagina and cervix,<sup>2</sup> when 24.0 per cent positive cultures were obtained. It is well known that the trichomonads demand a medium which is not too strongly acid. In 18 of the 23 patients with positive cultures, the pH ranged from 4.55 to 6.38 and the average was 5.58, well above that for the entire series. Twelve of this group of 18 had discharges classified as Type III, 5 as Type II, and only two as Type I. In 8 of the patients with positive trichomonas cultures, monilia were also grown. The pH values in 4 of this group ranged from 4.92 to 6.21, and averaged 5.46.

#### SUMMARY

The glass electrode technique offers a rapid and convenient method for determining the pH at any desired level in the vagina. In late pregnancy the acidity is highest in the middle portion of the vagina, with the region just inside the introitus being somewhat less acid (see Table I), and the cervix and upper vaginal fornices having an alkaline or only slightly acid reaction. The latter situation is undoubtedly due to the admixture of cervical mucus.

The acidity variations observed in the middle vagina correlate roughly with the type of vaginal flora, and apparently with the content of the vaginal bacilli of Döderlein. The monilia are most frequently present in the more acid discharges, while the trichomonads are favored by a less acid reaction. Consistent with this observation, it is generally true that the fungi are most easily cultivated from the middle vagina and the trichomonads from the upper portions near the cervix. Reported variations in the vaginal pH and in the asymptomatic presence of the trichomonads and the monilia under similar conditions and in comparable groups of patients may be explainable on this basis.

#### CONCLUSIONS

Varying conditions obtaining at different levels in the vagina under the influence of physiologic factors must be considered in any discussion of vaginal acidity or of the type of flora observed. All of the variations in the vaginal flora cannot be explained by alterations of the vaginal acidity.

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## PALLIATIVE TREATMENT OF DYSMENORRHEA

### WITH ACETYLSALICYLIC ACID, PHENACETIN AND PROPADRINE HYDROCHLORIDE

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THE treatment of dysmenorrhea of any type has been difficult especially in young women just beyond adolescence whose mothers will not permit a complete examination. If an examination is permitted, it frequently requires an anesthetic and even then the mother ordinarily will not permit of any radical procedure which might possibly give relief. Moreover many of the procedures are unsatisfactory.

The many medicaments are offered based on two principles: sedation and analgesia, or relaxation of the smooth musculature. Sedatives and analgesics may relieve those mild cases without cramps, but leave the usual "hang-over" of mental depression. They are of little value in the severe cases, while nearly all of the antispasmodics upset the stomach markedly, cause excessive dryness of the mucous membranes, or else are not antispastic enough to be of value, besides necessitating the use oftentimes of hypodermic administration.

For this study, dysmenorrhea was divided into the usual broad classification of primary or functional, and secondary or organic. The functional or primary dysmenorrhea was further divided into: obstructive, hypoplastic, and constitutional. And while it is sometimes impossible to differentiate these clearly and there is marked overlapping, for the purpose of this study the cases have been placed definitely in one or the other of the classes.

It would seem then that anything which would produce relief from pain without any aftereffects should be more than welcome. If, in addition to this, the mental depression could be lifted, much would have been accomplished.

In this study a combination of 5 gr. of acetylsalicylic acid, 3 gr. of phenacetin, and  $\frac{3}{4}$  gr. of propadrine hydrochloride was used. The value of acetylsalicylic acid as an analgesic is well known. It probably has the least depressant action of any known analgesic with most individuals. It is, however, ineffective in severe pain, and especially cramplike pain. It is fortunately tolerated well by most persons and is practically nontoxic. Phenacetin while probably possessing more analgesic properties than "aspirin" is apparently much more depressing in its action, and seems to be especially so during the menstrual period. It also, like "aspirin," is not capable of relieving cramplike pains.

It was felt that the dosage noted of acetylsalicylic acid and phenacetin was small enough to cause but little depression and that the

propadrine hydrochloride was synergistic in that it increased the effectiveness of the other two ingredients, but counteracted any tendency to depression afterwards. In addition to this, it was felt, but not proved entirely, that the propadrine hydrochloride was a marked antispasmodic and decongestant without side effects, and with no possible chance for anuria or nausea. Black<sup>3</sup> and Boyer<sup>4</sup> both found propadrine hydrochloride far superior to ephedrine as an antispasmodic and much less toxic.

The cases were not selected for age or severity, nor for the duration of the condition, but rather as the usual run of patients seen in the office of the general practitioner. They were divided according to the classification given above. In most of the cases the results were reported not only by the patient, but by the mother or relative also, with especial regard to the reaction of the individual to others about her, the temper, depression, and irritability.

The patients were given three capsules daily (except in the terribly severe cases, when the patient received one every three hours) at the very first onset of distress, and continued until the third day of the period. Pain after the third day is not relieved well by this preparation and should lead one to suspect some organic lesion. The capsules were given the first month, then skipped the second month, then repeated the third month in an attempt to cover the variation that may be expected in some women.

#### DISCUSSION

After a study of 34 cases of primary dysmenorrhea and 4 cases of organic or secondary dysmenorrhea, patients ranging in ages from 14 to 44 years of age, it was very apparent that the combination of acetylsalicylic acid, phenacetin, and propadrine hydrochloride is more effective in the primary type of dysmenorrhea and, it seems, is more effective if taken immediately upon the appearance of symptoms. There is no explanation for the fact that the results are not as good during the last few days of the menstrual period, although generally this makes no difference, for most of the patients are free from pain at that time.

There is a marked effect within a few minutes after taking the capsule, and a few patients showed almost an exhilaration, although it was never enough to keep the patient awake. It has a definite beneficial effect upon the turgescence of the nasal mucous membrane and the light-headedness which is so often seen in women at the time of menses.

The same combination was used by substituting ephedrine for the propadrine hydrochloride; however the effect seemed delayed, and several patients could not tolerate it because of nausea. It also produced a marked tremor in many patients and this seemed to leave a slight after-depression. No nausea or tremor was observed in any of the patients when propadrine hydrochloride was used. A few have reported that the skin felt "goose pimply" for a short period, but that it gave them a sense of exhilaration.

TABLE I. PRIMARY DYSMENORRHEA

NO.	AGE	COMPLAINT	FIRST MONTH	SECOND MONTH	THIRD MONTH	COMMENT
<i>Neuralgic or Nervous Type</i>						
1	34	Ache and depressed	Relief for 2 days	Usual pain	Relief for 2 days	No effect on time or clotting
2	22	Mild cramps and depression	Complete relief	Usual pain	Complete relief	No effect on time or clotting
3	26	Severe cramps	Partial relief, no loss of time	Usual pain	Partial relief, no loss of time	No effect on time or clotting
4	19	Delayed, cramps	Relief of pain	Usual pain	Relief of pain	Still delayed
5	26	Severe cramps, depression	Complete relief	Usual pain, depression	Complete relief	No delay or change
6	16	Severe cramps	Partial relief, in bed one day	Usual pain, in bed 3 days	Relief, not in bed	No effect on flow
7	22	Pressure and depression	Complete relief	Usual pressure	Complete relief	Period lessened 1 day
8	14	Cramps and irritability	Relief from cramps	Usual symptoms	Relief from cramps	Excessive flow and still irritable
9	16	Cramps	Relief from cramps	Usual cramps	Complete relief	No change at all
<i>Obstructive or Mechanical</i>						
10	34	Cramps and depression	Complete relief	Usual symptoms	Complete relief	No effect on time or clotting
11	21	Severe cramps, loss of 2 days	Relief, no loss of time	3 days' loss with cramps	Relief, no loss of time	One day less
12	16	Severe cramps, excessive flow	Complete relief	Usual symptoms	Relief from cramps	No change in flow, still excessive
13	26	Backache and pressure	Relief from pain and pressure	Usual symptoms	Relief from pain and pressure	Still has excessive flow, retroversion
14	24	Backache and pressure	Relief from pain and pressure	Usual symptoms	Relief from pain and pressure	No effect on time, anemic. Retroversion
15	14	Cramps and excessive flow	Relief from cramps	Usual symptoms	Relief from cramps	Still has excessive flow, retroversion and stenosis
16	37	Severe cramps	Partial relief	Severe cramps	Partial relief	Cervical repair which left stenosis
17	41	Cramps and depression	Relief	Usual symptoms	Relief	Beginning menopause
18	39	Leg ache and back ache	Relief first day	Usual symptoms	Relief first day	Three pelvic operations
19	40	Leg ache and hysteria	Partial relief	Usual symptoms	Relief, no hysteria	Cervical repair which left stenosis

TABLE I—CONT'D

NO.	AGE	COMPLAINT	FIRST MONTH	SECOND MONTH	THIRD MONTH	COMMENT
<i>Hypoplasia of Generative Organs</i>						
20	32	Pain after period starts, irregular	Partial relief	Usual symptoms	Partial relief	Infertile, infantile uterus
21	39	Severe backache	Some relief	Usual symptoms	Partial relief	Acute antifixation, long cervical neck, obese
22	14	Cramps and irregularity	No relief	Usual symptoms	Partial relief	Obese, lethargic and unsanitary
23	15	Cramps, epilepsy depression	Relief from cramps	Cramps, 1 seizure	Relief from cramps	No seizure during months while taking preparation
24	26	General pain and severe depression	Relief from pain and depression	Depression, usual pain	Relief from both	Loses 2 days. None lost while taking preparation
25	27	Amenorrhea, but pain and depression	Relief from pain and depression	Usual symptoms	Relief from pain	Has patent cervix. Periods 6 mo. Pain each month
26	37	Backache and hysteria	Partial relief	Usual symptoms	Partial relief	Long, antifixated uterus. Fear of pregnancy
<i>Dysmenorrhea Due to Constitutional Disease</i>						
27	19	Pelvic and backache	Partial relief	Usual symptoms	Partial relief	Incipient tuberculosis. In bed
28	39	Severe abdominal pain and leg ache	Slight relief	Usual pain	Slight relief	Active tuberculosis. Laparotomy 5 yr. ago
29	26	Malaise and depression	Complete relief	Usual depression	Complete relief	Anemic, chlorotic, hypothyroidism
30	39	General body aching	Fair relief	Usual aching	More relief	Marked hypoparathyroidism. Loss of calcium in bones
31	29	Severe cramps, excessive flow	Marked relief	Usual cramps	Marked relief	Severe arthritis, but improving
32	44	Severe cramps	Relief	Usual cramps	Relief	Change of life. Arthritis in all joints
<i>Migraine Type</i>						
33	23	Severe cramps, migraine	Relief, no attack	Cramps, pain headache and nausea	Relief, no attack	Always had migraine type of pain and headache and nausea
34	42	Aching and migraine attack	Relief, no attack	Usual symptoms	Relief, no attack	Migraine type of headache with nausea

TABLE II. ORGANIC OR SECONDARY DYSMENORRHEA

NO.	AGE	COMPLAINT	FIRST MONTH	SECOND MONTH	THIRD MONTH	COMMENT
1	33	Backache and leg ache	Partial relief	Usual symptoms	Partial relief	Large body uterus, with lacerated cervix
2	43	Severe backache	Partial relief	Usual symptoms	Partial relief	Endometritis and cervicitis
3	29	Backache	Partial relief	Usual symptoms	Relief	3 pelvic operations
4	29	Pelvic pain and backache	Partial relief	Usual pain	Partial relief	Subinvolution, cervicitis. Endometritis

A study was undertaken to determine what effect this preparation might have upon blood pressure. The patient was required to lie down for fifteen minutes during which time the blood pressure was carefully checked. One capsule of the preparation was then given orally, and the blood pressure checked every fifteen minutes for one hour and a half with the patient still lying absolutely quiet. No water or anything else was given and no one allowed in the room.

The patients were divided into three age groups: from 15 to 25 years; from 25 to 35, and from 35 to 45. It was found that variation in blood pressure was very slight, the greatest being 10 mm. of mercury in the systolic pressure at the end of forty-five minutes. This was the case of a young woman who was very excitable, who had a plus metabolic rate of 22 points. The average rise in pressure was four points, generally reaching this peak at the end of sixty minutes. All had dropped to normal at the end of ninety minutes. None displayed a compensatory fall below normal. The diastolic pressure varied not more than two points.

#### CONCLUSIONS

There are not enough cases in this study, nor could some of the features be well enough controlled to warrant drawing positive conclusions. However, this much is evident; this preparation offers marked relief for the majority of women who suffer distress and depression during the menstrual period. The relief from depression both physically and mentally is often more gratifying to the patient than the relief from pain. (1) It is safe and nontoxic. (2) Its effect is almost immediate. (3) It produces no nausea or dizziness, and no after effect. (4) It does not depress the kidneys, nor does it influence the regularity or the amount of the menstrual flow. (5) It appears to be most effective during the first two days of the period.

The preparation used for this study was made, upon request, by Sharp & Dohme of Philadelphia, Pa.

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## BLOOD STUDIES DURING PREGNANCY AND PUERPERIUM\*

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THE occurrence of a physiologic anemia developing during the course of pregnancy has been recognized. A 10 to 20 per cent lowering of hemoglobin may be the result of a hydremia associated with the increased vascular area which exists in pregnancy.

The etiology of the true anemias of pregnancy has not been proved conclusively. A number of factors play a role in the development of these anemias.

Strauss<sup>11</sup> believes that the vast majority of the anemias of pregnancy are of the hypochromic variety which are due either to a direct dietary deficiency or to a deficiency conditioned by gastric anacidity, hypoacidity or associated defects in the presence of fetal demands for blood building materials. Peters and Van Slyke<sup>9</sup> conclude that there is an apparent diminution of the body's supply of hemoglobin. Bethell<sup>12</sup> believes that the anemias of pregnancy are due either to pre-existing iron depletion or to an inadequate intake of protein of high biologic value.

During a recent study of the anemias of pregnancy (Labate<sup>7</sup>), a group of 19 patients were subjected to more intensive study in order to determine some of the etiologic factors which were responsible for the development of the anemic state during pregnancy.

*Method.*—Nineteen pregnant women who entered the obstetric ward at Bellevue Hospital during the last month of pregnancy either for premature rupture of the membranes, false labor, or for observation remained in the hospital until after delivery. A red blood count, hemoglobin (Sahli), reticulocyte count, hematocrit, and plasma protein determination were performed on admission. These were repeated on alternate days during the remainder of the prenatal period and during the first ten days following delivery. A gastric analysis was done during the ante-partum period and again on the eighth day post partum. The results of the study of the gastric analyses have been reported in a previous communication (Labate<sup>8</sup>).

The hematocrit readings were obtained using the method described by Wintrobe.<sup>13</sup> Six milligrams of ammonium oxalate and 4 mg. of potassium oxalate per 5 c.c. of venous blood were used as anticoagulant. In this solution the volume of the erythrocytes remains unaltered (Heller and Paul<sup>6</sup>).

The plasma protein determinations were done by the falling drop method (Barbour and Hamilton<sup>1</sup>).

*Results.*—Eight patients who had a blood loss of 350 c.c. or more, at the time of delivery, were excluded from the present analysis. The average red blood count of the 11 remaining women rose from 3.47 million during the thirty-eighth week of pregnancy to 3.70 million in the fortieth week. The average hemoglobin also rose from 9.6 gm. to 10.16 gm. and the average cell volume from 34.7 to 37.7 per cent

\*This work was carried out by means of a grant from The Bovine Company, Chicago, Illinois.



during the same interval (Tables I and II, Fig. 1). The plasma proteins increased from 7.28 mg. per cent to 7.71 mg. per cent between the thirty-eighth and fortieth weeks.

On the day of delivery, there occurred a slight drop in the red blood count and hemoglobin, but a temporary secondary rise was noted on the second day post partum. This increase in red blood count and hemoglobin was lost on the fourth day, but thereafter a slow rise ensued. The red blood count resumed a practically normal level on the tenth day. The hemoglobin, however, remained 9 per cent below normal (Table I, Fig. 1). Dieckmann and Wegner<sup>5</sup> also noted that the hemoglobin, two weeks post partum, was 17 per cent below normal.

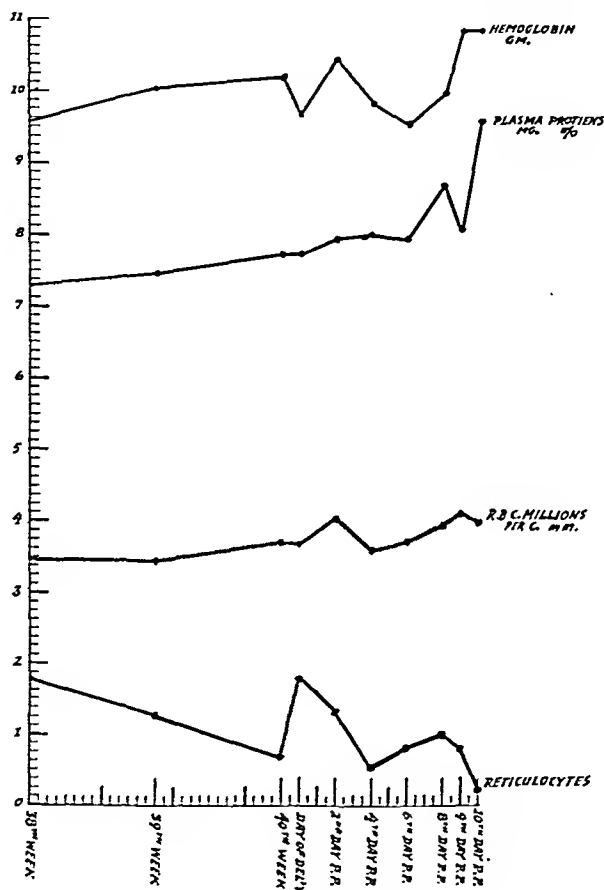


Fig. 1.

The cell volume following delivery continued to rise until the fourth day when a definite drop occurred. Thereafter the cell volume continued to show a steady increase until it rose to the normal level of 41 per cent on the tenth day post partum (Table II). Skajaa<sup>10</sup> found that in 14 women the cell volume increased steadily after delivery so that at from twelve to fourteen days it was normal at 43 per cent. The behavior of the cell volume in the puerperium probably represents the restoration of the normal physiologic relationship between the blood cells and blood plasma.

Although the cell volume rose to a normal level in the post-partum period, the mean corpuscular volume remained at a constantly high level, ranging between 100.6 and 104.1 cubic microns. This suggests that the higher value of the hematocrit is due, not to any alteration in the size of the individual red corpuscles, but to the greater number of packed cells per volume of blood. The amount of corpuscular hemoglobin remains unaltered. However, the mean corpuscular hemoglobin concentration is slightly below normal from the fourth to the eighth day post partum (Table II).

TABLE I. ANALYSES OF RED BLOOD COUNT, HEMOGLOBIN, HEMATOCRIT, PLASMA PROTEINS AND RETICULOCYTE COUNT IN THE LAST MONTH OF PREGNANCY AND PUERPERIUM ON 19 PREGNANT WOMEN

PERIOD OF GESTATION	RED BLOOD COUNT— MILLIONS PER C.M.M.	HEMO- GLOBIN GM. PER 100 C.C. BLOOD (SAHLI)	HEMATO- CRIT %	PLASMA PROTEINS MG. PER 100 C.C. BLOOD	RETICULO- CYTES
Thirty-eighth week	3.47	9.60	34.70	7.28	1.80
Thirty-ninth week	3.45	10.02	36.22	7.44	1.28
Fortieth week	3.70	10.16	37.07	7.71	0.66
Delivery day	3.66	9.63	38.25	7.72	1.80
Second day post partum	4.02	10.40	40.47	7.91	1.31
Fourth day post partum	3.58	9.83	36.90	7.98	0.53
Sixth day post partum	3.67	9.50	38.20	7.93	0.80
Eighth day post partum	3.89	9.92	39.90	8.69	1.00
Ninth day post partum	4.08	10.80	41.75	8.04	0.80
Tenth day post partum	3.94	10.80	41.00	9.56	0.20

TABLE II. ANALYSES OF THE HEMATOCRIT ON 19 NORMAL PREGNANT WOMEN IN THE LAST MONTH OF PREGNANCY AND PUERPERIUM

PERIOD OF GESTATION	HEMATOCRIT %	MEAN CORPUS- CULAR VOLUME IN CUBIC MICRONS	MEAN CORPUS- CULAR HEMO- GLOBIN IN MICROMICRO- GRAMS	MEAN CORPUS- CULAR HEMO- GLOBIN CONCENTRA- TION %
Thirty-eighth week	34.70	100.00	24.40	27.60
Thirty-ninth week	36.22	104.9	29.00	27.60
Fortieth week	37.07	100.10	27.40	27.40
Delivery day	38.25	104.50	26.20	25.10
Second day post partum	40.47	100.60	25.80	25.70
Fourth day post partum	36.90	103.10	27.40	24.00
Sixth day post partum	38.20	104.10	25.80	24.80
Eighth day post partum	39.90	102.30	26.00	24.80
Ninth day post partum	41.75	102.30	26.40	25.80
Tenth day post partum	41.00	104.10	27.40	26.30

TABLE III. ANALYSES OF STUDIES ON THE RED BLOOD COUNT, HEMOGLOBIN AND HEMATOCRIT ON 44 NORMAL PREGNANT WOMEN

RANGE OF R.B.C.	AV. R.B.C.	RANGE OF H.B.	AV. H.B.	RANGE OF HEMA. * %	AV. HEMA. %	RANGE OF M.C.V. * C. $\mu$	AV. M.C.V. C. $\mu$	RANGE OF M.C.H. * MICRO.	AV. M.C.H. MICRO.	RANGE OF M.C.H.C. * %	AV. M.C.H.C. %
3.89M.- 4.96M.	4.25M.	11.0 gm.- 14.55 gm.	12.23 gm.	32-45	38.9	74.4- 109.3	89.59	23.91- 37.00	29.25	25.3- 37.17	31.36

\*Hema., Hematocrit. M.C.V., Mean corpuscular volume. M.C.H., Mean corpuscular hemoglobin. M.C.H.C., Mean corpuscular hemoglobin concentration. Micro., Micromicrograms.

The plasma proteins were found to increase after delivery (Table I).

Normal values of the hematocrit have been reported variously. In the pregnant woman, Skajaa<sup>10</sup> gives 36.4 per cent as the average normal. Dieckmann and Wegner<sup>5</sup> report an average of 38.1 per cent between the thirty-sixth and fortieth weeks and 40.1 per cent between the tenth and twenty-fifth days post partum.

Wintrobe<sup>13</sup> found the range of the mean corpuscular volume in the nonpregnant woman to be 80 to 94 cubic microns, with an average of 87. In the pregnant woman Dieckmann and Wegner<sup>5</sup> determined the range of the mean corpuscular volume to be 80 to 100 cubic microns.

In order to determine normal values of cell volume and mean corpuscular volume for this study, hematocrits were obtained on 44 normal pregnant women. The range of the cell volume was found to be 32 to 45 per cent, with an average of 38.9 per cent. The range of the mean corpuscular volume was 74.4 to 109.3 cubic microns, with an average of 89.6 cubic microns (Table III).

### DISCUSSION

The increase in plasma proteins and hematocrit in the post-partum period probably results because of the readjustment in blood volume which follows delivery. DeLee<sup>3</sup> and Williams<sup>12</sup> believe that the blood volume increases during pregnancy and decreases during the puerperium. Dieckmann and Wegner<sup>4</sup> also found that the plasma and blood volumes begin to increase in the first trimester of pregnancy, and at term there occurred an average increase of 23 per cent in blood volume and 25 per cent in plasma volume.

The increase in the plasma proteins, cell volume, and erythrocyte count in the puerperium without a rise in reticulocytes, suggests that hematopoiesis is not the factor producing the rise in the red blood count. Furthermore, the rapidity with which the increase in the erythrocyte count takes place favors the idea of concentration rather than hematopoietic activity. That the increase in the red blood count, in the puerperium, may be due to concentration, occurring as the result of fluid loss with subsequent readjustment of blood volume, is further suggested by the fact that during the period of observation prenatally, no noticeable rise in the erythrocyte count and hemoglobin could be obtained in a number of patients showing a mild form of anemia. In a recent study (Labate<sup>7</sup>), it was found that treatment with 1 gm. of ferrous sulfate daily caused an increase in the red blood count from an average of 3.63 million to 3.88 million, and in hemoglobin from an average of 9.54 gm. to 11.17 gm. It was impossible to produce any further increase above these levels, in spite of intensive treatment with ferrous sulfate, parenteral liver, and a high protein diet. Nineteen of these patients were under constant observation on the obstetric ward during this period of intensive therapy. In those instances where hypoacidity of the gastric juice was demonstrated, dilute HCl was given orally without any effect.

It is apparent, therefore, that the diminution in the red blood count and hemoglobin in many of the mild forms of anemia, seen during pregnancy, may be due to dilution resulting from an increase in blood volume. These, then, represent physiologic and not true anemias of pregnancy. Bethell<sup>2</sup> came to the conclusion that, with the hematocrit as a basis for calculation and on the assumption that there occurs no compensatory output of erythrocytes, the lowest red blood count that may be

explained solely by hydremia is approximately 3.7 million and the lowest hemoglobin about 11.3 gm. (70 per cent).

The true anemias of pregnancy were found to respond quickly to iron therapy. One gram of ferrous sulfate daily is an efficacious dose. With this form of therapy on 325 pregnant women, the average red blood count rose from 3.68 million in the prenatal period to 4.09 million at the time of delivery. The average hemoglobin rose from 9.56 gm. to 11.61 gm. (Labate<sup>7</sup>).

#### CONCLUSIONS

1. The erythrocyte count, hemoglobin cell volume, and plasma proteins show a definite rise during the first ten days following delivery. The reticuloocyte count remains at a low level.

2. Whereas the red blood count rises to normal within the first ten days post partum, the hemoglobin remains 9 per cent below normal.

3. The cell volume also rises steadily in the puerperium to a normal of 41 per cent by the tenth day.

4. The increase in cell volume is not associated with any increase in mean corpuscular volume or mean corpuscular hemoglobin.

5. The plasma proteins rise steadily in the puerperium.

6. The increase in cell volume and plasma proteins and the rapid rise in the erythrocyte count in the post-partum period is due to concentration occurring as the result of fluid loss with consequent readjustment of blood volume.

7. Some of the mild forms of anemia developing during pregnancy are due to physiologic readjustments and do not represent true anemias.

8. The true anemias of pregnancy respond well to 1 gm. of ferrous sulfate daily.

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**Binet, A., and Canel, R.:** Hypogastric Sympathectomy for a Case of Incurable Cancer of the Uterus, Bull. Soc. d'obst. et de gynéc. 27: 109, 1938.

A case of inoperable carcinoma of the uterus is reported in which the authors performed a hypogastric sympathectomy. The result was excellent even though there was an extension of the disease into the parametria. The authors believe that in some cases chemical sympathectomy will yield as good results as surgical sympathectomy.

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# TRANSVERSE PRESENTATIONS

WITH A REPORT OF 24 CASES INCLUDING ONE OF "CONDUPLICATO CORPORE"

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**A**MONG about 20,000 labors, there were 24 patients with transverse presentation of the fetus, all delivering at term except 3 at eight months. Two others were recorded at seven months' premature labor that necessitated version and extraction. Thirteen of these were colored and 11 were white women. The population of this city here is 40 per cent negro and 60 per cent white. The incidence, therefore, is greater in the negro women than in the white, occurring once in 615 negro deliveries and once in 1090 white deliveries. The white people here are predominantly Anglo-Saxon. The records revealed that all were married. One white and one colored woman were pregnant with twins.

*Age Incidence.*—Eleven white women ranged from 18 to 34 years of age, 4 of these were from 20 to 25 years, and 4 were in the age group of 31 to 34 years. Thirteen colored women were from 20 to 40 years of age, 8 of whom were in the third decade.

*Parity.*—Only 2 were primiparas, one white woman 18 years old and one colored woman of 20. One white woman had had 10 children, one 6, and one 5. The others had one to three each.

*Complications.*—Prolapse of fetal hand and arm occurred in 13 cases; no prolapse in 11 cases. Five patients had hypertension, the highest blood pressure being 170/120 mm. Hg. Three patients had induction of labor by catheter insertion, 2 for hypertension and 1 for pyelitis. Five patients had albuminuria at time of labor, and 2 had pyelitis, 1 case of which developed after delivery.

LENGTH OF LABOR	MOTHER	FETUS	L—LIVED
			D—DIED
0- 6 hr.	5 lived	D L L L D	
6-12 hr.	8 lived	(Twins L D)	L L (Twins L L)
		D D D D	
12-18 hr.	3 lived	L L L	
18-24 hr.	3 lived	L L D	
24-36 hr.	1 lived	L	
48 hr.	1 died	D	
76 hr.	1 lived	L	
"Long and exhausting"	1 lived	D	
"Several days"	1 died	D	

*Management.*—In general, nonneglected patients, in labor less than twenty-four hours, were treated by version and extraction after com-

plete dilatation of the cervix. Two of these had the cervix dilated by Voorhees' bag of large size, a procedure highly recommended. Forceps to the aftercoming head was used in 3 cases. With this treatment there were no maternal deaths, a low grade sepsis rate of 5 per cent, and a fetal mortality rate of 40 per cent. Five patients were considered neglected, i.e., in labor longer than twenty-four hours. Two of these were delivered by version and extraction. One of the mothers and her baby lived. The other one was a colored woman, 40 years old, in labor several days, with a fetal arm out and macerated. She was delivered by version and extraction through an incompletely dilated cervix, following which she went into surgical shock and died within twenty-four hours, probably from rupture of the lower uterine segment. Preliminary use of a large bag probably would have saved her life. Three patients were delivered, 2 by embryotomy (decapitation) and the third, spontaneously, by *conduplicato corpore*. The case records of these 3 are appended.

CASE 1.—A colored woman, medium to obese constitutional type, aged 29 years, para v, gravida vi, at term, entered the hospital from a long distance with history of labor of forty-eight hours' duration. She had transverse presentation of a 7 pound 14 ounce infant with prolapsed left arm and right foot, with the fetal head above the pelvic brim to the left. The body was wedged in the pelvis and there were no signs of life in the fetus. Treatment included decapitation of the fetus by Braun's hook method. Examination revealed no tears in the cervix or in the fundus. Nevertheless this method entails severe bruising trauma to the lower uterine segment. The time required for this operation by this method in this case was one hour, and in spite of postoperative blood transfusions, the patient developed sepsis, with chills on the second and third days, lasting twenty to twenty-five minutes each. On the twelfth day she developed pneumonia and died on the twenty-first day. From this experience an original set of instruments was devised to reduce the time and trauma in future instances of this kind, and the next case report illustrates the use.

CASE 2.—A colored multipara, of medium to obese constitutional type, aged 38 years, para viii, gravida ix, with all children living, entered the hospital from a distance. She was near term, pregnant with twins, the lower one apparently dead with macerated left hand and forearm at the vulva. The head was to the left and above the pelvic brim. The body was wedged into the pelvic inlet. The second baby was in good condition. She had been in labor ten hours. The treatment instituted was decapitation of the first twin by an original method as follows: The obstetrician's left hand could be inserted into the cleansed and draped vagina far enough to get the index finger partly around the dead child's neck. A sterile 18-inch length of lead tubing, outside diameter  $\frac{1}{4}$  inch, inside diameter  $\frac{1}{8}$  inch, was inserted underneath the finger which bent it to conform to the cervical curvature. As the pliable tubing was inserted farther the upper curved end returned on the lower side of the neck. It was a simple matter to replace the lead tube with No. 13 piano wire which was then used as a snare through a brass tube and the head neatly and quickly severed from the body, leaving no jagged points of bone. The body then was easily removed, as was the head which was somewhat macerated. The live twin then was turned by the feet and extracted. Examination revealed a 2 cm. lateral laceration of the cervix which was sutured with catgut.

The time of anesthesia by cyclopropane was thirty minutes. The mother and the second child recovered and went home on the seventh day. While this patient was not in the desperate condition of the one reported above, the difference in time required for the two operations, the difference in trauma, and the variation in facility of performance are much in favor of this procedure.

CASE 3.—A colored woman, aged 24 years, para ii, gravida iii, attended the prenatal clinic once or twice. She went into labor on about the date calculated from her last menstrual period, and she was delivered in her home by the student obstetricians. The first stage of labor lasted eight hours and ten minutes, at the end of which time the membranes ruptured spontaneously and a male fetus weighing 3,118 gm., macerated, and so much softened that the bones felt like beans in a bean bag, was delivered in fifteen minutes. The report of the delivery stated that the "Right shoulder delivered first, the head to the left, and completely flexed on the chest, followed, then the left shoulder, these came out at a slight angle deviating somewhat to the mother's right. The trunk followed immediately with the legs, which were extended. The arms were along the sides of the body. The birth occurred very rapidly after the shoulders came down, all of the fetus coming out with one pain very much as a half congealed jelly might be poured out of a container. The head was so macerated and flexed that the three of us thought for a moment that no head existed. The cord was blue black, twisted, and around the fetus' neck. The placenta was seen to be lying in the vaginal orifice and fell out easily when touched. It was necrotic. The fetus had been dead about two weeks. The mother was in very good condition and made an uneventful recovery."

The placenta weighed 569 gm. The mother's blood was Wassermann negative, her urine was normal, and the blood pressure was normal until after probable death of the fetus, then 150/80.

#### SUMMARY AND COMMENT

In this study transverse presentation at term and in labor occurs once in about 615 negro deliveries and once in 1,090 white deliveries, with an incidence ratio in negro and Anglo-Saxon women of 10 to 6. There is a high incidence in multiparas and in twin pregnancies.

An arm prolapsed is found in about 55 per cent of cases. If in labor more than twenty-four hours, a patient so afflicted may be considered neglected.

The usual and very successful treatment in nonneglected patients is version and extraction after complete dilatation of the cervix. An original method of fetal decapitation in neglected patients is described. In order to be certain of how the baby lies, an x-ray study should be made before operation. In the nonneglected patients, the maternal mortality is negligible with low sepsis rate. The fetal mortality is about 40 per cent. Both mortality rates rise rapidly in the neglected patients.

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Benthin, W.: *Prontosil for the Treatment of Septic Conditions in Gynecology*, Med. Klin. 34: 1347 and 1490, 1938.

Benthin is skeptical about the benefit of *prontosil* in cases of sepsis but he is enthusiastic about the value of this drug in cases of puerperal and postabortal endometritis. He is in favor of using *prontosil* prophylactically in all febrile puerperal conditions and in all cases where there appears to be a threatened infection. The drug should be given early. *Prontosil* is the best drug of its group and is the least dangerous. The drug may be given rectally, hence can prevent the giving of painful injections.

In spite of the use of *prontosil*, every known means of treating puerperal infections should be employed at the same time.

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# PATHOLOGIC AND CLINICAL ASPECTS OF ADENOMYOSIS AND ENDOMETRIOSIS

## A SURVEY OF 224 CASES

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ADENOMYOSIS and endometriosis† have been the object of numerous investigations. Many points are, nevertheless, still controversial. It seemed, therefore, worth while to report the data of 224 specimens which were examined in this laboratory during a period of almost ten years.

It is not my purpose to discuss the various theories concerning the genesis of adenomyosis and endometriosis. I shall rather confine myself to a report of the figures and facts and to an attempt at interpreting them as far as they permit.

### INCIDENCE AND LOCALIZATION

From 1930 to 1939 approximately 16,000 surgical specimens were examined. Among them were 1,807 uteri which presented the following principal lesions:

	NO. OF CASES		NO. OF CASES
Myomas	1424	Benign tumors (except myoma)	13
Hyperplasia of myometrium	238	Metastatic carcinoma	3
Prolapse	88	Sarcoma	3
Carcinoma of body of uterus	37	Chorionepithelioma	1

Adenomyosis and endometriosis were found in 224 instances or in 12.4 per cent of the extirpated uteri.

The localization of the lesions was as follows:

Myometrium	152	Broad ligament	1
Ovary	41	Serosa of appendix	2
Tubal angles	12	Abdominal scar	1
Serosa of uterus	7	Bladder	1
Pelvic serosa	6	Round ligament (extraperitoneal)	1
			<hr/> 224

Adenomyosis, therefore, represented almost 70 per cent of the cases. The same incidence was reported by Frankl and Counsellor, whereas Jeffcoate, Seitz, and others stated a higher percentage of endometriosis. They probably paid more attention to endometriosis on account of its greater clinical significance. Furthermore, the criteria for diagnosing ovarian endometriosis are not uniform (King). Adopting the criteria used by Seitz the incidence of ovarian endometriosis would almost be doubled.

Among 380 autopsies of women between 20 and 55 years of age, 2 cases of adenomyosis and 1 case of endometriosis were found.

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†The terminology proposed by O. Frankl has been adopted. "Adenomyosis" designates the invasion of the myometrium by cytogenic tissue and endometrial glands from within the uterus; "endometriosis" means the presence of endometrium-like structures outside the uterus or invading the uterus from without.



## AGE DISTRIBUTION

Adenomyosis: (152 cases)

	21-30	31-40	41-50	51-60	61-
No.	3	40	96	12	1
Per cent	2	26	63	8	

Six women, or 4 per cent, were under 35 years of age, 96 per cent were older than 35, and 72 per cent were older than 40 years. The average age was 46, the mean age 44; the youngest patient was 24, the oldest 63 years.

Ovarian endometriosis: (41 cases)

	21-30	31-40	41-50	51-
No.	12	22	6	1

Thirty per cent were under 30, 54 per cent were under 35 years of age, 19 per cent were older than 40. The average age was 33, the mean age 36; the oldest patient was 57, the youngest 22.

The difference in age incidence is evident. While adenomyosis belongs definitely in the second half of the generative period, endometriosis occurs in women at the height of their sex life.

The adenomyotic structures were of the "resting" type in the patients who were not menstruating any more. In these cases no histolysis was present. This may be ascribed to the decrease in ovarian function connected with the menopause.

An attempt was made to correlate the severity of the lesions with the age of the patient. The invasion of the myometrium was slight in 44 per cent of the women under 40, but only in 24 per cent of the patients between 40 and 50, and in only one case in a woman over 50. These figures demonstrate that adenomyosis is a progressive lesion and that it starts after 35 years of age in most instances.

These differences in age distribution point clearly to a different mechanism in adenomyosis and endometriosis.

## COMBINATION OF ADENOMYOSIS AND ENDOMETRIOSIS

Adenomyosis was combined with ovarian endometriosis three times and with other forms of endometriosis in three instances also. This rarity of the combination is another factor in suggesting a different origin.

## COMBINATION WITH OTHER PELVIC DISEASES

Adenomyosis was found together with myomas in 61 cases; with hyperplasia of the myometrium in 44 instances, and with myomas plus hyperplasia in 40 cases. There was postmenopausal atrophy of the uterus in 7 instances. A normal myometrium was found in not a single case. (A myometrium more than 2 cm. thick was considered hyperplastic.)

Endometriosis of the ovary was combined with myomas in 70 per cent of all cases.

Microcystic ovaries were present in 25 instances. This figure, however, may not be correct, because in cases in which only a hysterectomy was done, the data relative to the ovaries were sometimes not complete.

Adhesions were present in more than 50 per cent of the cases.

The high incidence of myomas is a universal feature of all statistics on adenomyosis and endometriosis.<sup>8, 9, 17</sup> Vice versa, in about one-seventh of the myoma patients, adenomyosis or endometriosis was found. This is by far more than the probable incidence. It has led Seitz and others to assume a common origin for these lesions. The investigations of Jeffcoate and Lipschuetz tend to support this point of view.

All uteri which were not myomatous had a hyperplastic myometrium. Hyperplasia of the myometrium is usually found in multiparous women (Adler). This fact also strongly suggests a common factor in the genesis of hyperplasia of the myometrium and of adenomyosis.

Several authors have postulated a constitutional factor in the etiology of adenomyosis and endometriosis. As a possible indicator of some primary constitutional

deviation, the original menstrual history of the patient was studied. Only 26 out of 152 patients with adenomyosis had originally an abnormal menstrual cycle. In all the other cases the menstruation was originally "normal." Of the 41 patients with endometriosis of the ovaries, only 7 had originally disturbed menstruation. The first menstruation occurred at the normal age in these patients. It was not delayed, as Frankl noticed in his cases.

### CARCINOMA AND ADENOMYOSIS OR ENDOMETRIOSIS

The possibility of carcinomatous degeneration seems very likely indeed if one considers the histolytic and hyperplastic activity of adenomyosis and endometriosis. However, only isolated cases<sup>6, 17</sup> have been reported. None of them has withstood R. Meyer's criticism. One of the two cases in our material was highly suggestive of carcinomatous change in adenomyotic lesions. No definite proof was possible.

Almost as rare is the coincidence of cancer and endometriosis.<sup>23</sup>

### STERILITY AND FERTILITY

In 140 cases of adenomyosis the distribution was the following:

STERILE	ABORTIONS ONLY	1 PARA	MULTIPARA	UNMARRIED OR CONTRACEPTIVES	NO DATA
4	4	4	109	10	9
3%	3%	3%	78%	7%	6%

In 41 cases of ovarian endometriosis:

STERILE	ABORTIONS ONLY	1 PARA	MULTIPARA	UNMARRIED OR CONTRACEPTIVES	NO DATA
13	4	3	10	7	4

Of 18 patients with endometriosis (ovary excluded), 3 were sterile, 2 had abortions only, 4 were unmarried, and the others had 1 or more children.

Almost 50 per cent of the patients with adenomyosis had had more pregnancies than deliveries. Among the women with ovarian endometriosis only 4 gave a history of interrupted pregnancies.

The very low sterility index of adenomyosis was surprising. For comparison, two statistically suitable groups, each of 200 patients, were taken. The number of sterile patients in these groups was 10 per cent and 9 per cent, respectively. This is twice the incidence found in patients with adenomyosis. The percentage of women with abortions only was the same in the two control groups as in adenomyosis. There was, however, a remarkable difference in the number of childbirths. In the control group, 15 per cent and 24 per cent, respectively, had one child only, of the patients with adenomyosis but 4 per cent. On the other hand, the multiparas represented about 50 per cent of the control group and almost 80 per cent in adenomyosis. These figures highly suggest a possible role of repeated childbirth or abortions in the genesis of adenomyosis. The experimental production of adenomyosis by curetting the pregnant uterus tends to corroborate this assumption.<sup>24</sup>

The high sterility index in ovarian endometriosis has been stated universally.<sup>3, 8, 22</sup> Turunen frequently noticed hypoplasia of the sex organs in his patients. I was unable to verify his observation in our material.

Most statistics report previous pelvic or abdominal operations in up to 50 per cent of the cases with ovarian endometriosis. Only 6 of our 41 patients, however, had been operated upon previously. I do not know how to account for this difference.

### FUNCTIONAL CHANGES IN ENDOMETRIUM AND IN ADENOMYOSIS

Lack of space does not permit a discussion in detail of this interesting problem. The functional phase was found to be the same in the endometrium and in the adenomyotic structures in more than 50 per cent of the cases. In the majority of cases, the endometrium exhibited a normal picture corresponding to the phase of

## THE PLACENTA IN TOXEMIA OF PREGNANCY

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ONE of the chief obstacles in all investigation and research in the problem of toxemia of pregnancy lies in making the diagnosis clinically. Because a patient has hypertension, edema, and albuminuria during the pregnant state does not mean that she has toxemia. Also because she has had essential hypertension, chronic nephritis, or pyelonephritis previous to the pregnancy, does not mean that she will or will not have the superimposed toxemia. In this paper toxemia of pregnancy refers to the effect of pregnancy, in certain cases, on the renal-vascular system resulting in hypertension, edema, and albuminuria. This is irrespective of the presence or absence of previous kidney or vascular damage. Clinically it is often impossible to make the above distinction as there is no clinical or laboratory finding available to prove the point. With this state of affairs in mind, we have been trying to differentiate the various hypertensive states by pathologic study, following the birth of the child.

Fortunately few of these women die and therefore pathologic diagnosis of kidney and liver lesions is rarely available. However, during the past twenty years we have gathered together a series of 24 autopsies<sup>1</sup> from our own and other hospitals in which we have made complete pathologic studies. From this group of autopsies, we have come to the conclusion that there is a definite kidney lesion which can be described as a glomerulonephrosis which is present in all cases of true toxemia. In contrast to previous reports, we have been able to find the characteristic liver lesion of hemorrhagic necrosis in only half of the cases. Therefore to us the kidney lesion seems the more important.

Due to the scarcity of autopsy material, some years ago we started studying the placenta as the only tissue available in most cases. We hoped to find some lesion typical of toxemia which would definitely classify the cases. We believed that we found such a lesion and reported it as such.<sup>2</sup> We have continued this work and still believe that we have a method of distinguishing true toxemia. At first we thought that we could distinguish between true toxemia and chronic nephritis. However, we soon discovered that some patients with chronic nephritis showed the lesion of toxemia and others did not. We, therefore, have come to the conclusion that we can distinguish between chronic nephritis and chronic nephritis with toxemia, but that all cases with or without previous kidney damage have the same placental lesion if they have the superimposed toxemia of pregnancy. Essential hypertension and pyelonephritis in pregnancy show no changes in the

cycle of treatment. Ten fistulas occurred among those patients who had received their initial treatment elsewhere, and one in a patient receiving no treatment.

#### COMMENT

1. From a study of this group of cases, we believe that every patient with carcinoma of the cervix should have a thorough clinical investigation.

2. Treatment of such patients should not be undertaken unless all the personnel and facilities necessary for the treatment are available.

3. Except for the extent of the disease, the initial treatment is the most important factor in determining the ultimate result.

4. Inquiry as to extent of disease and the factors used at the initial treatment in some of the patients who have been referred for secondary treatment has disclosed a deplorable lack of information.

5. X-radiation should not be used as the sole method of treatment except in advanced cases where only palliation is to be expected.

#### SUMMARY

1. From Feb. 1, 1928 to Dec. 1, 1934, 136 patients with carcinoma of the cervix were seen. Of these, 122 were treated and 26 have remained well for at least five years, an absolute cure rate of 19.1 per cent and a relative cure rate of 21.3 per cent. With one exception, these patients were treated exclusively by radiologic methods.

2. The best results were obtained by combined x-ray and radium.

3. The interval between the appearance of the first sign and the patient's first visit to a physician averages five and one-half months.

4. The interval between the first visit to a physician and the first pelvic examination averages two months.

5. The interval between the first pelvic examination and the institution of cancer treatment averages three and one-half months.

6. There is an average delay of eleven months between the appearance of the first sign and the initiation of cancer treatment.

7. While the patient is consulting a physician more promptly after the appearance of the initial sign, there does not appear to be any shortening of the interval between the first visit and the first pelvic examination.

8. A large number of the patients were treated for cancer before coming to us and were given more treatment by us because the disease had not been controlled.

9. In 69 patients the treatment was initiated by us, and 22 of these lived five years or more, a cure rate of 33.3 per cent.

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(For discussion see page 988.)

all of the cases showing widespread placental damage, a large amount of albumin was present. Whether or not there is any relation between the physiology of placental degeneration and albuminuria cannot be stated. However, from this study, albuminuria seems to be the most important sign of the amount of toxic damage going on in the placenta. In the early placental lesions (40 cases), albumin appears in less than half. This would indicate that the placental damage begins before clinical signs of the condition appear. How closely related to the cause of the toxemia the placental damage may be, is hard to say, because there must be some factor causing the degeneration.

TABLE I

BLOOD PRESSURE	EDEMA	ALBUMIN*
<i>Definite Placental Lesion, 60 Cases</i>		
120-140	Slight or none	None
23%	23%	11%
140-160	Definite	S.P.T.
26%	51%	12%
160-240	Marked	H.T.
51%	26%	77%
<i>Beginning Placental Lesion, 40 Cases</i>		
120-140	Slight or none	None
42%	37%	55%
140-160	Definite	S.P.T.
37%	39%	25%
160-240	Marked	H.T.
21%	24%	20%

\*S.P.T., slight possible trace; H. T., heavy trace.

Blood pressure in relation to syncytial degeneration does not seem to be nearly as constant as albumin. About one-half of the cases of true toxemia have a systolic pressure of 160 mm. of mercury or less; while one-quarter are under 140. This is also shown by the fact that 3 out of the 12 patients in this series with convulsions had a blood pressure of 140 or less. Of the 51 per cent of these patients with pressures over 160, the actual height of the blood pressure bore no definite relation to the actual condition of the patient. In the series of early cases the blood pressure averaged considerably lower than in the severe cases. However, over half of them were over 140 systolic and several of them ran as high as in the other series. These cases that ran a very high blood pressure with mild toxemia were largely of the group with previous hypertension. This is the point that is most confusing in the clinical judgment of these cases. If we had a basic blood pressure taken over a period of time previous to the pregnancy, it would be of immense importance. The rise in blood pressure during pregnancy is of much greater important than the actual level.

The amount of edema present is difficult to judge. As it depends upon the observations of different people, no standard can be laid down. Swelling of the feet and moderate swelling of the hands is so common as to be frequently disregarded. Edema in other parts of

placenta unless there is a superimposed toxemia. The characteristic placental lesion as previously described consists primarily of a premature aging of the placenta. As has been known for many years, the full-term placenta shows a certain amount of syncytial degeneration. This is normal and physiologic. On further investigation we found that this involved from 10 to 50 per cent of the small terminal villi. We then noticed that in toxemia the majority of the villi were involved and in the severe pre-eclampsies and eclampsies all of the small villi may be involved. In normal seven and eight months' placentas, there is little or no syncytial degeneration; but in seven and eight months' toxemic cases, there again was 50 per cent or more syncytial degeneration. The type of syncytial degeneration is quite characteristic. In its first stages it consists of the clumping together and autolysis of the nuclei in the syncytial cytoplasm (not the syncytial buds), leaving clumps of darkly-staining masses with no cell outlines and wide areas of syncytial cytoplasm without nuclei. The final stage is the disappearance of all nuclei from the syncytial layer, leaving the villus surrounded by a thin irregular layer of hyaline material. It is a lesion that can be easily recognized after sufficient study of normal syncytium. The type of fixation of the material, the stain and the thickness of the cut sections all affect the picture and therefore should be standardized before comparing the normal with the abnormal.

In addition to the above lesion we have noticed a marked congestion of the villus blood vessels in the toxemic cases. The blood vessels are distended with blood occupying most of the villus. The cause for this is hard to explain. Certainly if one regards the syncytium as similar in function to the glomerular epithelium of the kidney, the destruction of this epithelium plus circulatory congestion might easily explain the high fetal mortality in this condition. The lack of permeability of the damaged syncytium to products required by the fetns, including oxygen, might well injure the fetus severely.

With the above criteria in mind, we are now making a report on 100 cases of toxemia of pregnancy. We shall try and correlate the placental lesion with the clinical, laboratory, and endocrine findings available in these cases. We were very fortunate, in that, 60 of the cases in this series were studied in conjunction with Drs. Soma Weiss and Lewis Dexter of the Thorndike Memorial Laboratory. Their work<sup>3</sup> consisted in observing the cases during pregnancy. Following delivery they made complete clinical and laboratory studies of these patients for the purpose of diagnosis and classification. They have kindly given us permission to quote some of their findings in this paper.

The first part of our study is shown in Table I. This is a comparison of cases classified by the placental lesions against the clinical findings of blood pressure, edema, and albuminuria. The outstanding point shown by the table is that the presence of albumin in the urine is most closely correlated with the placental findings. In 90 per cent of the 60 cases showing a definite placental lesion, albumin was present. In

TABLE III\*

	TOXEMIA WITHOUT PREVIOUS HYPERTENSION 26 CASES	TOXEMIA WITH PREVIOUS HYPERTENSION 17 CASES	PREVIOUS HYPERTEN- SION UNINFLUENCED BY PREGNANCY 16 CASES
Placenta toxic	82%	96%	35% (borderline)
Placenta normal	18%	4%	65%

\*From Weiss and Dexter.

terest. In the group of toxemia without previous hypertension, the diagnosis agreed in 82 per cent. The majority of the cases in which the placenta was found normal was in the borderline group with a very moderate rise in blood pressure and little or no albuminuria. This type of case is a very mild form of toxemia, if it be called such, and one would not expect to find any marked pathologic change. In the second group of toxemia with previous hypertension, the placental diagnosis was in marked agreement with the clinical one. This is important as it is this group of cases that offers the most difficult prognosis as far as their obstetric career is concerned. Finally, in the last group of cases, hypertension previous to pregnancy was established. From the medical point of view no toxemia was present during pregnancy. Some of these cases showed a high blood pressure and considerable albumin. They would be considered toxemic by the obstetrician. Yet their hypertension was present before and after pregnancy and the patient survived with no material change in her general condition. The answer to this cannot be settled as yet. It is important that in this group the majority with marked hypertension before, during, and following their pregnancy showed no toxic change in the placenta. This does show that in many cases pregnancy has little or no effect on the patient with previous marked hypertension. This observation is of great importance to the clinical obstetrician. The five cases of this group which showed toxic placenta were so borderline, both from the clinical and placental findings, that the diagnosis could have been made either way.

#### SUMMARY

A study of toxemia of pregnancy has been made with the purpose of correlating the placental pathology with the clinical and laboratory findings. Also a titration of the prolan of pregnancy in both the placentas and urines has been done. Sixty of the cases in this review have been studied by the medical service as well as the obstetric. From the results obtained, it is felt that the placental lesion is an accurate indicator of the severity of the toxemia. The placental lesion is found in cases with no previous hypertension or kidney damage. It is present in many cases with previous renovascular disease. Therefore, toxemia is an entity in itself which may either appear with an undamaged kidney or may be superimposed upon previous kidney damage. Albuminuria is the most accurate sign of the presence of placental damage. A titration of the prolan of pregnancy, both of the placenta and of the urine, shows no standard difference between normal and toxemic cases. The medical classification of hypertension in pregnancy agrees largely with the

the body is of more value, particularly of the face and abdominal wall. In this series there seems to have been somewhat more edema observed in the advanced than in the early cases. There are cases in both groups where edema was not observed and the amount of marked general edema seems to be about the same in both groups. Therefore edema is a somewhat vague observation and much less to be relied upon than the albuminuria.

Using our placental classification of toxemia, we have extracted several normal and toxic placentas for their content of prolan of pregnancy. We have also done urine extractions on the same contrasting groups. The findings are given in Table II. A survey of the figures

TABLE II

NORMAL PLACENTA*	PROLAN TOXIC PLACENTA		URINE PER 24 HOURS	
			NORMAL	TOXIC
4,000 R.U.	1,000 R.U.	Eclampsia	200 R.U.	1,000 R.U.
2,500	540	Eclampsia	1,000	1,000
500	1,515	Eclampsia	1,000	1,000
500	1,000	Eclampsia	750	500
1,000	660		1,000	500
500	660		200	500
330	500		1,000	2,500
660	1,000		660	1,000
500	1,000		330	1,000
330	1,000			1,000
	660			1,000
				500
				1,000
				200

\*R.U. per kilo wet tissue.

will show that while some normal placentas run a lower level of prolan than that of the toxic group, this is not always the case. Individual normal cases show even larger amounts of prolan than any of the toxic group and many of the toxic cases have as little as many of the normal cases. We have been unable to establish a definite level below or above which the prolan reading will show a normal or a toxemic case. In observing the urinary prolan we have found no significant difference between the total prolan of the normal and the toxic groups. This agrees with the work of Taylor and Seadran<sup>4</sup> who were unable to demonstrate any constant increase in the prolan content of the serum or urine in toxemic cases. Smith and Smith,<sup>5, 6</sup> have reported a higher prolan content in toxemia, as have other investigators.<sup>7</sup> The difference in results must rest on the problem of what cases are truly toxemia of pregnancy. Until there is some generally accepted basis of classification contrary results will continue to appear.

A study of 60 cases of this series has been made by Weiss and Dexter.<sup>8</sup> Their diagnosis was made following a complete medical and laboratory study with past history and follow-up. They have divided their cases in three groups as shown in Table III. Against their final diagnosis we have put out placental findings. The results are of considerable in-



c. A third view indicates that trichomonas and some bacterium may both be responsible, one producing the initial tissue changes necessary and the other being a secondary invader.

II. What pathologic changes occur in the condition known as trichomonas vaginitis?

III. Is *Trichomonas vaginalis* a species distinct from *T. intestinalis*?

Similar questions have occurred with reference to the role of *T. intestinalis* in diarrheic conditions with which it is often associated. One opinion holds that it may be the cause of the diarrhea, while the other maintains that *T. intestinalis* is merely a commensal which appears in great numbers, because the environment is especially suitable for its rapid multiplication. The fact that carriers of the intestinal trichomonas also occur is used as evidence against the pathogenicity of *T. intestinalis*. On the other hand, kittens naturally infected with trichomonas have been found to exhibit dysenteric symptoms, and it also has been possible to induce diarrhea and dysentery in kittens by experimentally infecting them with *T. intestinalis* of man (Kessel, 1928).

Penetration of the trichomonads into the mucosa of the intestine was observed in some of the infected kittens, though such penetration was rare, a catarrhal-like inflammation with the presence of a diphtheritic membrane being the usual picture produced. Subsequent study of the intestinal mucosa of human cases positive for *T. intestinalis* has shown the occurrence of similar surface pathology but failed to show the presence of trichomonads within the tissue.

#### OBSERVATIONS IN THE PRESENT STUDY

Material utilized in the present study was collected from patients presenting symptoms answering to the clinical description of trichomonas vaginitis and from whom *T. vaginalis* was recovered.

The results of our observations may be considered under three headings.

1. *Pathology.*—The occurrence of an irritating frothy vaginal discharge often with an offensive odor was common to the cases considered in this study. Upon examination, the walls of the vagina were usually found to be injected and tender, presenting in some instances a pronounced hyperemia often exhibiting minute points of hemorrhage. In the more advanced cases granular areas were prominent.

Serial sections of biopsy material taken from these areas of hemorrhage and granulation were studied and show the following general appearance:

a. The surface mucosa in areas is covered with coagulated material in which trichomonads, leucocytes, and red blood cells are commonly found (Fig. 1). The surface epithelium is usually intact but in certain areas shows erosion with the migration of flagellates between the surface cells. Areas of hemorrhage are also occasionally observed to break through the surface epithelium.

b. In the subepithelial layer, areas of intense infiltration are found, consisting of lymphocytes, some polymorphonuclear leucocytes and a few plasma cells (Fig. 3). These areas show increased vascularity, extending in some instances to the basement membrane and in others to the surface epithelium.

c. In some instances definite necrosis appears within these areas of infiltration, the process extending toward the surface (Fig. 4). Usually it has not been possible to find trichomonads in these early areas of infiltration. In the areas which have become definitely necrotic (Fig. 5), it is often possible to find the flagellates (Fig. 2), and, in one case in which the mucosa had entirely eroded, they were seen between the cells in the subepithelial layer.

placental findings except in some cases with previous hypertension in which there was a very early placental lesion with no marked clinical signs of toxemia.

# CONCLUSIONS

1. Toxemia in pregnancy can be accurately judged by placental histology.

2. Albuminuria is the most trustworthy sign of the extent of the toxemia.

3. Toxemia is an entity present either with or without previous kidney damage.

4. Titration of the prolan of pregnancy is not an accurate sign of the presence of toxemia.

The authors wish to express their appreciation for the technical assistance of Miss Estelle L. Donovan and Miss Jean A. Berger.

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330 DARTMOUTH STREET

## OBSERVATIONS ON THE PATHOLOGY OF TRICHOMONAS VAGINITIS AND ON VAGINAL IMPLANTS WITH TRICHOMONAS VAGINALIS AND TRICHOMONAS INTESTINALIS

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IN THE consideration of vaginitis with which trichomonas is usually associated, several important questions with reference to etiology, epidemiology, and pathology occur which still require investigation. Among them are:

I. What is the etiologic agent of the condition known as trichomonas vaginitis?

a. The most generally accepted belief is that *Trichomonas vaginalis* is the primary etiologic agent, although this contention has not been proved beyond question. It is based primarily on finding the flagellates in great numbers in the exudate and has not been subjected to exhaustive critical consideration.

b. A second theory considers that *T. vaginalis* is a commensal which multiplies rapidly in the suitable environment which is produced by some bacterium or other etiologic agent. A nonhemolytic streptococcus has been suggested by Hibbert (1933). Hesseltine (1933), and Hibbert and Falls (1938).

These findings indicate that the histopathology occurring in this type of vaginitis is not brought about alone by simple invasion of the flagellates from the lumen of the vagina but that there is some additional mechanism, either toxic or bacterial in nature which is responsible for the primary tissue changes or else that the flagellate is conveyed in some unrecognizable stage by the blood stream to the areas of infiltration and ultimate necrosis.



Fig. 4.—Later area of infiltration in subepithelium showing necrosis.



Fig. 5.—Areas of necrosis in subepithelium, the more advanced one showing presence of trichomonads.

**2. Cultural Studies.**—In order to look for some etiologic agent other than the flagellate and to compare the flora and fauna of normal vaginas with vaginitis cases, *T. vaginalis* exudates from cases of vaginitis and smears from normal vaginas were subjected to the following routine procedures: (a) Smear examination for trichomonas; (b) culture examination for trichomonas; (c) culture examination for fungi on Sabouraud's media; (d) culture examination on special media for: (1) members of the colon-typhoid-dysentery group of bacteria on eosin-methylene-blue plates, (2) streptococci in alkaline veal infusion broth, and (3) lactobacilli on whey agar; (e) stools from these patients were also examined for trichomonas.

Table I gives the results of these studies on 12 normal individuals and 33 vaginitis cases.

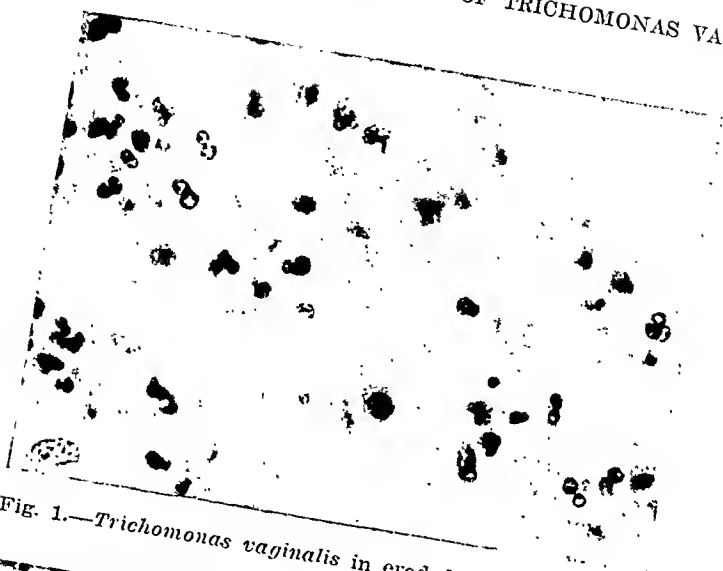


Fig. 1.—*Trichomonas vaginalis* in eroded surface mucosa.

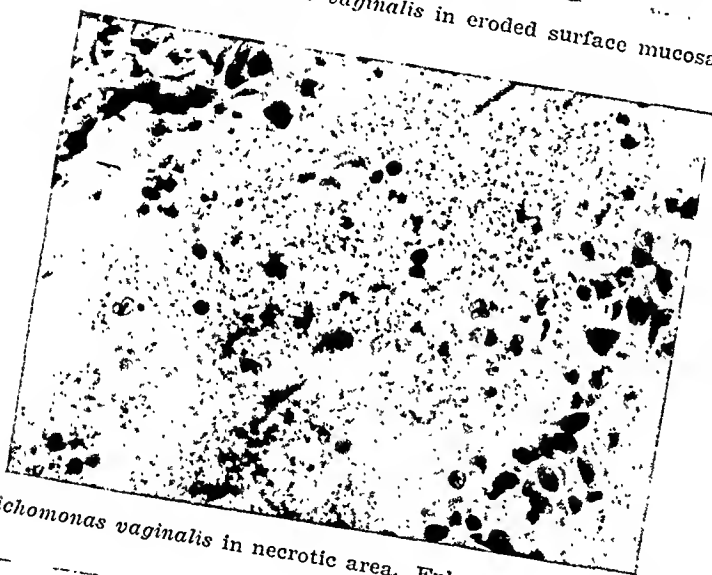


Fig. 2.—*Trichomonas vaginalis* in necrotic area. Enlarged lower area of Fig. 5.

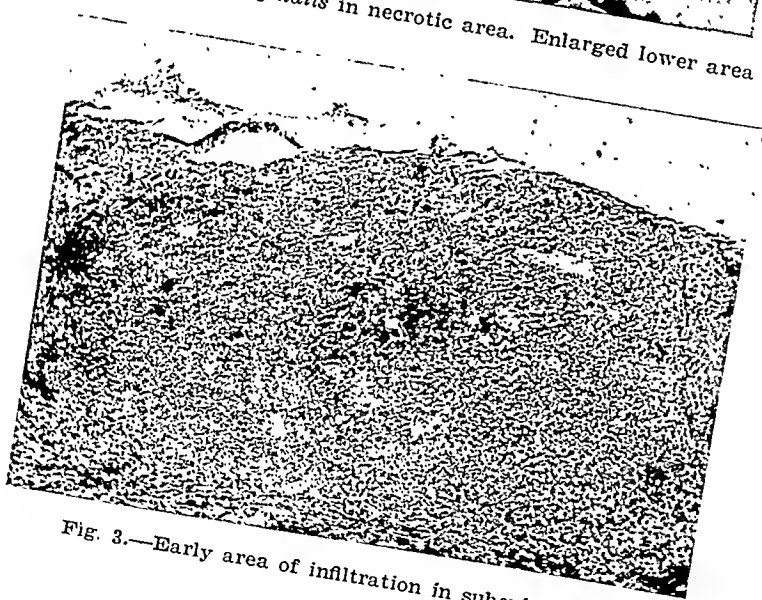


Fig. 3.—Early area of infiltration in subepithelium.

the menstrual cycle. Glandular hyperplasia was present in only 13 per cent. The endometrium, therefore, does not give any evidence of ovarian dysfunction in the great majority of the cases.

### SYMPTOMATOLOGY

Due to the frequent combination of adenomyosis with other pelvic disease, it is difficult to distinguish symptoms that are characteristic of adenomyosis. Excessive menstruation, with shortened interval, is considered the most important symptom.<sup>1, 4, 19</sup> However myomas as well as hyperplasia of the myometrium may cause similar symptoms. Jeffcoate, on the other hand, found metrorrhagia in 20 of his 26 cases.

In the present material, 92 of 138 patients complained of excessive bleeding. Fifty-four had hypermenorrhea, 27 polyhypermenorrhea, 4 had polymenorrhea, 4 had metrorrhagia. In many instances, however, the bleeding had become continuous for the last few weeks. No type of bleeding was found specific for myomas, myometrial hyperplasia, or adenomyosis.

Pain was complained of in 41 instances. It was dysmenorrheic in 16 patients, unrelated to menstruation and appearing as lower abdominal or back pain in 35 instances. The latter type was much more frequent in uncomplicated myometrial hyperplasia. Vaginal discharge, urinary disturbances and swelling of the abdomen were infrequent complaints.

Thirty-five of 41 patients with ovarian endometriosis complained chiefly of pain. Nineteen had dysmenorrhea of the acquired type, 16 had lower abdominal pain or backache unrelated to menstruation. Ten of the latter group had dysmenorrhea also. Thus, 29 altogether mentioned dysmenorrhea as chief complaint. This fact has been brought out by all authors. Uterine bleeding was present in 26 of these patients. It was menorrhagic in 24 instances; only 2 patients had metrorrhagia. As myomas were present in more than two-thirds of the cases, it remains doubtful what role the endometriosis played in the bleeding.

### CONCLUSIONS AND SUMMARY

One hundred and sixty-four cases of adenomyosis uteri and 60 cases of endometriosis have been studied.

Adenomyosis, in our material, is almost 3 times as frequent as is endometriosis.

Adenomyosis belongs to the second half of the generative period. Multiparity seems to be one causative factor. The sterility index is lower than normal.

In no case of adenomyosis was the myometrium found normal; either myomas or diffuse hyperplasia of the myometrium, or both, were present. This seems to point to a common, possibly hormonal, etiologic factor.

Glandular hyperplasia was found only in one-eighth of the cases of adenomyosis. In about 50 per cent, the adenomyotic glands presented a picture similar to those of the endometrium. Absence of histolysis indicates inactivity of the adenomyotic process.

Persistent hypermenorrhea with dysmenorrhea in multiparous women between 35 and 50 years of age may be considered suggestive of adenomyosis. The frequent combination with other uterine diseases renders the preoperative diagnosis difficult.

Ovarian endometriosis occurs in younger women between 25 and 40 years of age, usually. Primary and secondary sterility are frequent. In 70 per cent of the cases myomas were present. Gynecologic operations have been carried out previously in a few cases only.

The menstrual cycle has been originally normal in the majority of women with adenomyosis and endometriosis.

TABLE I. FAUNA AND FLORA OF NORMAL VAGINAS COMPARED WITH TRICHOMONAS VAGINITIS CASES

	NORMALS (12 CASES)		VAGINITIS (33 CASES)	
	+	-	+	-
<i>T. vaginalis</i>	0	12	30	3
Fungi	0	12	2	31
<i>Escherichia coli</i>	3	9	8	25
Streptococcus	12	0	33	0
Diphtheroids	12	0	33	0
Lactobacillus (Döderlein's bacillus)	7	5	3	30
After treatment			22	11
Stool examination for <i>T. intestinalis</i>	0	12	1	32

A. It will be observed that *T. vaginalis* was found in none of the normals in this series while it was found in 30 of the 33 who exhibited clinical vaginitis symptoms. The flagellate has been found, however, in a few instances in this study in which no characteristic vaginitis symptoms were apparent. These would represent the carrier state, which condition has been reported by other workers.

B. *Trichomonas intestinalis* was not found in the feces or vaginal smears of the 12 normals of this series and was found only once in the feces of the 33 patients who had trichomonas vaginitis. This flagellate is present in about 3 per cent of all stools examined in the Los Angeles County Hospital.

Four patients who harbored *T. intestinalis* examined during this period and who showed no signs of a vaginitis were examined for *T. vaginalis*. All were negative.

C. No fungi were found in the normal individuals and monilia was found only twice in the vaginitis cases.

D. No nonlactose-fermenting rods were encountered in either group, and *Escherichia coli* was found in 33½ per cent of each group.

E. Alpha streptococci similar in morphology to those commonly encountered in the intestinal tract (Kessel, 1936) but affording slightly different carbohydrate reactions were always present both in the normals and in the patients with vaginitis.

F. Diphtheroids also were present in both groups.

G. Lactobacillus, probably the same organism designated by some as Döderlein's bacillus, was recovered by culture from 7 of the 12 normals but only from 3 of the 33 clinical cases before treatment. After treatment and the disappearance of the clinical symptoms, this same organism was recovered from 66½ per cent of these individuals. This observation supports the opinion that the presence of aciduric bacteria may be used as an index of a healthy vagina.

These cultural studies indicate that *T. vaginalis* is usually associated with cases of trichomonas vaginitis but that no one bacterium or fungus isolated to date is associated more frequently with such vaginitis symptoms than with normal individuals.

3. *Transmission Experiments.*—Transmission experiments were of three types:

A. *Human vaginal implants as shown in Table II:*\* These were carried out on human volunteers whose vaginas were cultured both for bacteria and trichomonas prior to the implants. The series is small and does not warrant drawing final conclusions. It affords, however, some pertinent observations.

(a) All 3 cases into which exudate was implanted directly from cases of trichomonas vaginitis subsequently developed characteristic symptoms of vaginitis and two weeks after the implant *T. vaginalis* was recovered from them. Patients were treated after the fourth week.

\*Observations in the current study support the view held by many observers and summarized by Wenrich and his coworkers (Bland and others, 1932) and Powell (1936) that morphologic differences exist between *T. vaginalis* and trichomonas from the intestinal tract. Trichomonads designated as *T. intestinalis* conformed to usual descriptions of trichomonas from the intestine and those designated as *T. vaginalis* to their description of this species.

TABLE II. VAGINAL IMPLANTS\*

	NO. OF CASES	RESULTS			
		TRICHOMONAS		VAGINITIS	
		+	-	+	-
Direct smears from trichomonas vaginitis cases	3	3	0	3	0
Culture of <i>T. vaginalis</i> containing bacteria	3	3	0	2	1
Bacteria only	3	0	3	1	2
Cultures of <i>T. intestinalis</i>	3	0	3	0	3

\*All cases negative symptomatically and negative for trichomonas by smear and culture before implants were made.

(b) All 3 cases into which laboratory cultures of *T. vaginalis* were implanted showed the presence of the flagellate in the vaginas two to four weeks after the implant. Only one, however, developed characteristic vaginitis symptoms. These cultures had been carried in the laboratory by frequent subculturing over a period of six weeks before the human implants were made. They contained the bacteria which remain stabilized in the protozoan culture which in this instance consisted of a gram-negative rod, of the escherichia group and an alpha streptococcus.

(c) A mixture of the above bacteria, free from trichomonas and of pure cultures of alpha streptococcus recovered from cases of vaginitis were implanted into three normal vaginas. One of these showed mild symptoms of vaginitis though no trichomonas were found. It should be noted that an occasional case of vaginitis, thought clinically to be trichomonas vaginitis, has been encountered in this study from which it has not been possible to recover *T. vaginalis*.

(d) Cultures of *T. intestinalis* were implanted into three normal vaginas. No trichomonads were recovered on follow-up examination two to four weeks later and no symptoms of vaginitis developed during this time.

**B. Vaginal Implants in Monkeys:** Since the reports of previous investigators on this topic are variable in their conclusions (see Hegner, 1928, 1929, 1934, Hegner and Chu, 1930, and Dobell, 1934), it was decided to attempt to transmit *T. vaginalis* and *T. intestinalis* to the vaginas of a series of 18 available monkeys belonging to the species *Macacus rhesus*. It was judged that the monkeys ranged from three to five years of age, all having begun the menstrual cycle. Notations were made at the first examination as to whether the animals were virgins or nonvirgins. The successful implants were obtained in 2 virgin and in 1 nonvirgin animal.

The feces of all monkeys were examined for *T. intestinalis* and all were found on the first or second examination to harbor this parasite. The vaginas of all monkeys were examined at least 5 times at intervals of one week before experimental implants of trichomonads were made and all were found to be negative for flagellates both by direct smear and by culture from each examination.\*

The method used in taking the vaginal smears was: (a) to clean the region around the vagina carefully by washing and by subsequent swabbing with an alcoholic cotton swab, and (b) to insert sterile nasal forceps into the vagina and by means of a sterile cotton swab, dampened with saline, to swab thoroughly the vaginal wall. Smears and cultures were then made from this swab. Implants were made by injecting exudate or culture containing the trichomonads directly into the vagina by means of a pipette, and then holding the monkey's head downward for several minutes in order that the injected material might bathe the vaginal walls.

\*Exceptions occurred in two examinations in which actual fecal material was found in the vaginas at the time of examination. Culture of this material yielded *T. intestinalis*, but when the examination was repeated three days later, the vaginas were negative for trichomonads.

A summary of the implants made and of the results obtained is found in Table III and may be summarized as follows:

a. Of 6 attempts to implant *T. vaginalis* contained in freshly collected exudate from a human case of trichomonas vaginitis to the vaginas of 6 monkeys, one produced positive results. The infection on the first and second weeks following the implant indicated marked multiplication of the flagellates which were found in great numbers among the epithelial cells from the vaginal wall. The third examination following the infection showed a marked decrease of flagellates, the same being detected by culture only. The fourth and subsequent examinations have demonstrated no flagellates. Subsequent implants of culture material containing *T. vaginalis* produced negative results with all 6 monkeys.

b. Of 6 attempts to implant *T. vaginalis* obtained from a human case of vaginitis and grown in Locke-egg serum culture media, into the vaginas of 6 monkeys, 2 produced positive results. The vaginal smears were heavily positive at the first examination one week after implant and have remained so for a period of twenty-eight weeks. No frothy discharge was apparent in the vaginas of these 2 infected monkeys though a marked cellular exudate was always present in the vaginal smears from these animals that was not observable in the uninfected monkeys. Two subsequent attempts to implant *T. vaginalis* from culture into the 4 negative animals of this series produced negative results.

TABLE III. ATTEMPTED IMPLANTATION OF *T. vaginalis* AND *T. intestinalis* TO VAGINAS OF *Macacus rhesus*

MATERIAL IMPLANTED	PREV. NEG. EXAMINA- TIONS	RESULTS			DURATION OF IN- FECTION
		+	-	%+	
Exudate from <i>T. vaginalis</i> vaginitis	5 weeks	1	5	25	3 weeks
Culture of <i>T. vaginalis</i> from case of vaginitis	5 weeks	2	4		28 weeks
Culture of <i>T. intestinalis</i> from human feces	5 weeks	0	6	0	—
Culture of <i>T. intestinalis</i> from monkey feces	10 weeks	0	8		—

c. Attempts to implant cultures of *T. intestinalis* recovered from human feces into the vaginas of 6 monkeys produced negative results. Two repeated attempts were also negative.

d. Attempts to implant cultures of *T. intestinalis* recovered from monkey feces into the vaginas of 8 monkeys produced negative results. Five of the monkeys, however, have been used in experiment (c) and 3 in experiments (a) and (b) recorded above and suggest the possibility of immunity to infection, which subject requires further investigation.

In summarizing these experiments one concludes that: (1) attempts to implant *T. vaginalis* recovered from human cases of trichomonas vaginitis into the vaginas of 12 monkeys, negative for *T. vaginalis*, were successful in 3 or 25 per cent of the instances and (2) attempts to implant *T. intestinalis* recovered from man into the vaginas of 6 monkeys and *T. intestinalis* recovered from monkeys into the vaginas of 8 monkeys, all resulted in failure. (3) Sixteen attempts have been made using methods similar to those employed by Kessel (1928) in transmitting *T. intestinalis* of man to kittens. All met with negative results.

# DISCUSSION AND CONCLUSIONS

*Etiology of T. vaginitis.*—The question of the etiologic agent of the clinical condition commonly known as trichomonas vaginitis is raised, and certain evidence is presented from studies of the histopathology and from implant experiments which indicates that the etiology of this condition is not as definite as is usually assumed and that some factor in addition to *T. vaginalis* may play a role in the production of clinical trichomonas vaginitis.



Early lesions in the submucosa fail to show the presence of trichomonads, while the later necrotic lesions often do.

Implants into normal vaginas of exudate from characteristic vaginitis cases which contained *T. vaginalis* and bacteria resulted in all instances in the occurrence of characteristic symptoms and in the recovery of the flagellates.

Implants of cultures containing *T. vaginalis*, *Escherichia coli* and an alpha streptococcus in one series and of these two bacteria in another, resulted in one clinical case of vaginitis in each series of three, though the case in which bacteria alone were implanted did not develop the characteristic severe symptoms ascribed to the usual case of trichomonas vaginitis.

*Relationship of T. vaginalis and T. intestinalis.*—Two conflicting opinions occur with reference to the relationship of *T. vaginalis* and *T. intestinalis*. (1) They are considered by some to be the same species and vaginal infections are regarded by some gynecologists as of intestinal origin. (2) By other workers they are regarded as different species, and it is considered that they cannot be transferred from the intestine to the vagina with facility.

In order to determine which of these theories is correct, it is imperative that conclusions be reached from studies made from the following approaches: (1) Morphologic comparison of the two organisms, (2) incidence of *T. vaginalis* in normal individuals and in cases of trichomonas vaginitis, (3) experimental implants of *T. vaginalis* and *T. intestinalis* to the human vagina, and (4) experimental implants of trichomonas in susceptible animals.

Observations in this study support the theory that *T. vaginalis* and *T. intestinalis* differ in several respects. Such conclusions are based on the following data:

1. They exhibit characteristic differences in general morphologic appearance and in their method of locomotion. Careful observations on this point have been made previously by Hegner (1925), Wenrich and his collaborators (1931, 1932), Stein and Cope (1931), Westphal (1935) and Powell (1936), and it would seem that any one who cares to look for the differences they record can observe them.

2. Incidence of *T. vaginalis* and *T. intestinalis* in nonvaginitis cases as compared with cases of trichomonas vaginitis. *T. vaginalis* has been consistently encountered in the vaginal smears of patients suffering from vaginitis while *T. intestinalis* does not show a higher incidence in the intestinal tract of vaginitis cases than of normals. Cases positive for *T. intestinalis* do not show an incidence of *T. vaginalis* higher than that reported in the general population.

3. *T. vaginalis* is easily transferred experimentally from one human vagina to another, while all attempts in this series of experiments to transfer *T. intestinalis* to the human vagina have resulted in failure. This is consistent with carefully executed attempts reported by others.

4. Attempts by previous investigators to implant trichomonads into the vaginas of monkeys have not met with uniform results. The earlier work of Hegner and his associates raises questions of interest but does not solve them. Hegner's last report (1934) indicates that *T. intestinalis* may live temporarily in the vagina of monkeys but that no evidence of multiplication was obtained. Dobell (1934) records a single instance of successful implant of a trichomonas from the human intestine into the vagina of a monkey. The infection in man was previously acquired experimentally from a monkey. Since Dobell does not state whether the trichomonas with which he was dealing was *T. vaginalis* or *T. intestinalis* (*T. hominis*) an accurate interpretation of his results is impossible.

The present report, using a larger series of monkeys than used by previous authors, supports the view that *T. vaginalis* of human origin may be experimentally established and multiply in the vaginas of monkeys and that *T. intestinalis*, either of monkey or of human origin may not be established in the vaginas of monkeys. The authors realize that even this series is too small to warrant the drawing of indisputable conclusions but feel that the results are significant.

5. *T. intestinalis* of man can be successfully implanted into the intestinal tract of kittens as shown by Brumpt (1925), Eisele (1926), Kessel (1926) and Bonestell (1936). On the other hand attempts to transmit *T. vaginalis* to the intestinal tract of kittens have resulted in failure in studies reported by Kessel (1933) and by Bonestell (1936).

The evidence reported in this study supports the theory that *T. vaginalis* and *T. intestinalis* (*T. hominis*) are distinct species, since they exhibit both morphologic differences and environmental differences. These data contradict the contention of some gynecologists that the trichomonads found in vaginas are of intestinal origin.

#### SUMMARY

Serial sections of biopsies from areas of hemorrhage and granulation in cases diagnosed clinically as trichomonas vaginitis are described. They indicate that the pathologic change occurring in this type of vaginitis is not produced alone by simple invasion of flagellates from the lumen of the vagina, but that some additional mechanism exists, either toxic or bacterial in nature which is partially responsible for primary tissue changes.

Implants into normal vaginas of exudate from cases of trichomonas vaginitis containing *T. vaginalis* and bacteria resulted in the occurrence of characteristic vaginitis, while implants of cultures of *T. vaginalis* and bacteria produced only one case of typical vaginitis and implants of *Escherichia coli* and an alpha streptococcus in culture produced only a mild vaginitis without characteristic discharge.

Experimental implants of *T. vaginalis* to human and monkey vaginas resulted in infection while attempts to infect human and monkey vaginas with *T. intestinalis* ended with negative results. These facts fail to support the theory that the trichomonads that infect the vagina are of intestinal origin.

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## PREGNANCY AND COARCTATION OF THE AORTA

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THE term coarctation of the aorta implies a constriction of the vessel in the region of the insertion of the ductus arteriosus or its vestige. Bonnet has divided cases into infantile and adult types. In the infantile form there is a narrowing of the aorta between the origin of the left subclavian artery and the insertion of the ductus arteriosus, the region termed the fetal isthmus. In the adult type there is a constriction of varying degree about the insertion of the ductus.

In 1760 Morgagni called attention to the condition. In 1791, according to Barie, Paris described the first authentic case.

Blackford gives the incidence of coarctation of the aorta as approximately 1 in 1,550 cases as obtained from necropsy figures. At the time of publication of his 200 cases, only 19 had been diagnosed during life, indicating the frequency of overlooked diagnoses. In the various series reported there is a predominance of males over females in ratios varying from 2 to 1 to as high as 3 to 1.

*Pathogenesis.*—Several theories have been advanced relative to the pathogenesis of this condition. Those of syphilitic infection, thrombophlebitic propagation along the ductus, and ductal involution involving the aortic wall, have for the most part been abandoned. Syphilis is a rare associated finding and the disease could hardly occlude a lumen of such dimensions as the aorta. Brunner described ductal tissue joining that of the aortic wall and continuing into it but Walkoff failed to confirm this continuity. In coarctation, the finding that the ductus may be patent throughout or open at either end, made it obvious that ductal obliteration could not account for all cases. At present the most widely accepted theory is that of intrauterine anomalous development at the site of the fourth aortic arch as originally proposed by Rokitansky and others. This is borne out by the finding of associated local and general anomalies.

*Pathology.*—Coarctation of the aorta occurs in varying degrees from an abrupt ligature-like constriction, to localized hypoplasia. The entire aorta is hypoplastic in about 10 per cent of cases. In rare instances the external configuration may be normal with complete occlusion of the lumen by stenosis or a membrane. Localized thinning of the wall with dilatation above and below the site of coarctation is described. Meixner's sections have shown destruction of the elastica with connective tissue replacement. Localized atheromatous and mycotic changes occur with occasional aneurysmal formation. The *Streptococcus viridans* is the

most common offending organism in the mycotic process. The collateral circulation depends on the anastomoses between the branches of the subclavian, aortic intercostal, and epigastric arteries, and the elaboration of anomalous vessels which would otherwise not have been called on to function. Tortuous dilated intercostal arteries erode the lower rib margins. In Abbott's series 18 out of 200 cases had associated cardiac anomalies, one of the most common being a bicuspid aortic valve of the developmental type found in 25 per cent. Cardiac hypertrophy was present in 75 per cent, most commonly involving all chambers and individually the left ventricle. Generalized vascular and somatic abnormalities are frequently associated. Cerebral aneurysms resulting from increased pressure on inherently defective vessel walls have been described by Turnbull.

*Diagnosis.*—This is based on the presence of all or some of the following: Evidence of collateral circulation, although this may be entirely absent clinically. Pulsating vessels may be found along the courses described, most frequently in the interscapular area where there may be a thrill and systolic murmur, the latter rasping in character, likened by Bochkalek to the placental souffle. Hallock has called attention to isolated suprasternal pulsations. Notching of the inferior rib margins may be seen on x-ray (Rösler's sign).

The coarctation may sometimes be visualized in the left oblique position. The aortic knob may be small or absent, and the ascending aorta dilated. In the upper extremities there is almost always a hypertension with high pulse pressure. King found normal pressure in the left arm and hypertension in the right which he attributed to the proximity of the left subclavian artery to the site of coarctation. In the lower extremities there is a relative hypotension with decreased to absent pulsations in the abdominal aorta and its branches. Bonnet has shown that these pulsations depend on the route taken by the blood in returning to the aorta rather than on the volume of blood flowing through them. If the blood is returned immediately by the intercostals the pulsations tend to be more pronounced. Blumgart has investigated the dynamics of the circulation. Ordinarily the pulsation in the femoral artery starts 0.01 second after that in the brachial artery, but where the blood follows a devious course this interval may be prolonged to 0.05 second. The blood supply to the lower extremities was within normal limits. It was pointed out that the arteriolar pressure in the legs could be raised only by elevation of the arterial pressure which depended upon increased aortic pressure above the site of coarctation, and this in turn could be accomplished only by increased cardiac work. Accordingly, one of the earliest symptoms of cardiac failure was intermittent claudication.

Grollman and Ferrigan studied cardiac output and found normal arteriovenous oxygen differences but a slightly increased cardiac output which they attributed to the increased metabolism.

Cardiac enlargement may be present. A long rasping systolic murmur may be heard over the entire precordium transmitted along the course of the aorta. Exophthalmic goiter is sometimes associated and has been attributed to the increased blood supply to the gland, resulting from the collateral circulation.

Essential hypertension, intrathoracic tumors, aneurysms, and exophthalmic goiter have been confused with coarctation of the aorta.

*Prognosis.*—The outcome of this condition presents a most disheartening picture. About 75 per cent of the patients die by their fortieth year, and, of these, about 75 per cent succumb to cardiovascular causes. There are isolated instances of individuals with coarctation surviving to the ninth decade. In Blackford's series 147 out of 196 died as a result of the lesion; 68 of gradual cardiac failure, 16 from sudden cardiac failure, 38 from rupture of the aorta, 25 from cerebral hemorrhage, and 6 from endocarditis or aortitis.

A survey of the literature has yielded 26 cases of coarctation of the aorta in pregnancy. Three additional cases are presented. The previously reported are summarized in Tables I, II, and III.

In the New York Lying-In Hospital, during the past seven years there have been three recognized cases of coarctation in approximately 31,000 obstetrical patients.

TABLE I. DEATHS DURING PREGNANCY OR SHORTLY THEREAFTER

AUTHOR	AGE	PARITY	GRAVIDITY	COL-LATERAL CIRCULATION	BLOOD PRESSURE	CARDIAC ENLARGEMENT	EKG	NOTCHING RIBS	PERIPHERAL PULSATATIONS	OUTCOME
Fawcett	45	viii	ix	--	--	+	--	+	--	Death from cardiac failure 14 days post partum. Autopsy revealed complete atresia of aorta at insertion of patent ductus, fused aortic valves, thin atheromatous aortic wall
Strassman	25	i	ii	+	--	+	--	--	--	Death from rupture of aorta at end of pregnancy. Autopsy revealed dilated aorta with smooth intima, aortic valves thickened
Kreigh	28	ii	iii	+	--	+	--	--	--	Hemiplegia in seventh month and death from another cerebral accident in ninth. Autopsy revealed moderate stenosis of aorta at insertion of obliterated ductus and hypoplastic proximal aorta
Katz	25	i	ii	--	--	0	--	--	--	Death from rupture of aorta into pericardium at end of pregnancy. Autopsy revealed extreme stenosis at insertion of patent ductus, dilated aorta with smooth thin walls, and normal valves
Hallock and Hebel	31	v	vi	+	--	0	LAD	0	--	Death from endocarditis several months following normal delivery. Autopsy revealed moderate stenosis with mycotic aneurysm above, bicuspid aortic valves covered with fresh vegetations, splenic and renal infarcts

TABLE II. CASES IN WHICH PREGNANCY HAD A DELETERIOUS EFFECT

AUTHOR	AGE	PARITY	GRAVIDITY	COLIAT- ERAL CIRCULAT- ION	BLOOD PRESSURE	CAR- DIAC EN- LARGE- MENT	EKG	NOTCH- ING RIBS	PERIPH- ERAL PULSA- TIONS	OUTCOME
Weinberg and Gartenlaub	38	i	ii	+	RA 130/100 LA 240/120 RL 150/100 LL ?	+	LAD	+	Decr.	Fainting attacks and bedridden for 6 months after first pregnancy; then well for 8 years until second pregnancy; when she developed precordial pain, dyspnea and thyrotoxicosis which persisted after normal delivery. Subsequent thyroidec- tomy with some relief
Eppinger and Midelfart	28	0	ii	+	RA 300/125 LA 290/130 RL 135/100 LL 110/ 90	+	LAD	+	Decr.	Cerebral accidents, precordial pain, epistaxis, ver- tigo, headaches, scotomas, dyspnea and fainting during pregnancies both resulting in abortions
King	25	ii	-	--	RA 122/ 66 LA 122/ 60 RL 104/ 90 LL 108/ 90	0	Neg.	0	Decr.	Severe throbbing headaches during both preg- nancies
King	24	0	i	+	A 160-210 90-100 L 110-140 70-80	0	--	+	--	Precordial pain and dyspnea since childhood, worse during pregnancy. Blood chemistry and renal function normal. Low forceps delivery, normal puerperium. Told to avoid further pregnancies
Maxwell	34	iv	v	+	Arm 245/160	--	--	--	Decr.	Dyspnea and ankle edema since childhood. Seen in fifth month with aggravation of above plus head- ache, scanty urine and albuminuria. Improved with bed rest, subsequent course not given
Laffont and Laffargue	24	ii	iii	--	--	+	--	--	Decr.	Edema and severe dyspnea fourth month, miniature section and tubal sterilization. Febrile course requiring digitalis. No signs of cardiac failure one month later.
Lian, Abaza and Frumusan	19	0	i	+	--	+	Neg.	+	Decr.	Dyspnea after onset of pregnancy and severe at- tacks of syncope. Therapeutic abortion third month. Course not given
Lian, Abaza and Frumusan	30	0	i	--	--	+	--	+	--	Cardiac failure following birth of child. Course not given

TABLE III. CASES WITHOUT EVIDENCE OF UNTOWARD EFFECT OF PREGNANCY

AUTHOR	AGE	PARTY	GRAVIDITY	COLLAT- ERAL CIRCUL- ATION	BLOOD PRESSURE	CARDIAC EN- LARGE- MENT	EKG	NOTCH- ING RIBS	PERIPH- ERAL PULSA- TIONS	OUTCOME
Strassman	57	vii		+	--	+	--	-	---	Found dead from cardiac failure. No history of obstetrical difficulties. Autopsy revealed complete stenosis, smooth intima, and normal valves
Gossage	53	xiii		0	--	0	--	-	Present	Suffered a hemiplegia many years after last pregnancy. Course not given
Weber and Price	56	xi		+	230 190	+	--	-	---	Death from rupture of aneurysm in neck. No past obstetric difficulty. Last pregnancy 12 years previous. Aorta showed atheromatous changes
Leudet	37	iv		+	--	+	--	-	Deer.	Death from rupture of aorta. No past obstetric difficulties. Extreme stenosis of aorta without dilatation or atheromatous changes
Abbott	38	i		-	--	-	--	-	---	Death from congestive failure. No obstetric difficulty
Brunner	30	i		+	--	0	--	-	---	Death from pulmonary tuberculosis. Pregnancy one year previous without difficulty. Aorta obliterated by internal septum below insertion of patent ductus. Proximal aorta hypoplastic with atheromatous changes. Valves normal
Blackford	22		i	+	RA 168/94 LA 164/90 RL 102/88 LL 98/84	0	Neg.	-	Deer.	Miscarriage at 6 months without previous symptoms. Diagnosis confused with exophthalmic goiter. Course not given
Haberer	47	vii		+	--	+	--	-	---	Death from complications of transverse myelitis resulting from pressure of dilated artery. No past obstetric difficulties. Complete stenosis of aorta at site of obliterated ductus. Dilatation of proximal aorta. Bicuspid aortic valve
Van den Berg	29	iv		+	250	+	--	-	Deer.	No obstetric difficulties. Course not given
Evans	45	ii		+	A 205 120 L 85/7	+	--	+	Absent	Shortness of breath, precordial pain, hyperthyroidism, dilated ascending aorta. No past obstetric difficulties. Course not given
Hamilton and Stewart	22		i	+	--	+	--	+	Deer.	Uneventful pregnancy and labor. Course not given
Troutman	45	ii		+	A 160-120 90-100 L 85/7	+	Neg.	+	Absent	Choking and dyspnea while under observation. One miscarriage. No obstetric difficulties. Course not given
Caballero	31	iii		+	A 210 90	+	--	+	Absent	Two previous abortions. No obstetrical difficulties. Course not given

The two conditions are found together only rarely. They probably represent two different processes with some factors in common.

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## AN ATTEMPT TO CONTROL FETAL WEIGHT

## PRELIMINARY REPORT

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EXCLUDING prematurity, most neonatal deaths occur in babies having a birth weight in excess of eight pounds (3,636 gm.). As the fetal birth weight curve rises above eight pounds (3,636 gm.) both the fetal mortality and maternal morbidity curves also rise. The relationship between maternal and fetal weight curves has never been clearly established; however, it is known that the two curves often fail to coincide, because there are factors which cause elevation of maternal weight without affecting fetal weight, the most common factor being edema.

Practically speaking, the maternal weight curve is followed throughout pregnancy to reveal early evidence of toxemia, as manifested by edema. Clinical investigation has proved that maternal weight can usually be controlled by dietary restrictions; however, these restrictions have no effect upon fetal weight.

Realizing that maternal dietary excesses do not cause fetal obesity, the most reasonable etiologic factor that presents itself is a disturbance in thyroid metabolism. Williams<sup>1</sup> states that hypertrophy of the thyroid can be recognized clinically in 65 to 90 per cent of all pregnant women. Before an organ undergoes hypertrophy there must first be an increased demand placed upon that organ. In the case of preg-



pressures: LA 230/110, RA 200/100, LL 125/110, RL 125/110. X-ray revealed enlargement of the left ventricle and scalloping of the ribs. Electrocardiogram revealed left axis deviation. Renal function tests and blood chemistry were normal. Because of the strong desire of the patient to bear children and the relatively advanced stage of the pregnancy, the patient is being carried to term under a strict regimen of rest and limited activity. At term delivery will be effected by cesarean section and tubal sterilization performed under open drop ether.

#### DISCUSSION

There are, in all, 29 patients with an average of about 3 children each. Five died during pregnancy or soon after delivery: 2 from ruptured aorta, 1 of cardiac failure, 1 of cerebral accident, and 1 of endocarditis. Ten patients surviving pregnancy were definitely made worse by it. In other words, in slightly over half of the cases reported (including ours), pregnancy evidently had a deleterious effect upon the condition.

It is apparent that patients with coarctation are in constant danger of sudden death or serious accident. As has been pointed out, there is a bicuspid aortic valve in 25 per cent of cases and the same is found in 50 per cent of cases with rupture of the aorta. The pathologic thinning of the aorta and other arteries, particularly the cerebral, has also been pointed out. Once the diagnosis is confirmed, unless the patient shows evidence of cardiac failure, the clinical findings are not necessarily related to the immediate prognosis. As has been stated, the sword of Damocles is constantly over the head of these unfortunate patients. The findings of the condition at autopsy in individuals dying suddenly may be a complete "surprise d'amphitheatre." Besides the vulnerable points listed above, the congenital lesion is a locus minoris resistentiae, and all chances of infection should be strictly avoided.

There can be little doubt that the strain of pregnancy and labor may either aggravate the condition or cause sudden death. Examples of both have been given above. If pregnancy can occur and maintain itself, it seems logical to assume that either the coarctation is slight, or if extensive, the collateral circulation must be adequate so that in each instance the uterus receives an ample supply of blood. It should be stressed again, however, that sudden death may occur in either instance.

Stander and Cadden found that the cardiac output increased 50 per cent in pregnancy, beginning about the fourth month. Cohen and Thomson found increase in cardiac output up to the ninth lunar month with subsequent decrease prior to labor at term. Therefore in the second and early third trimesters of pregnancy, one may expect to have the increased cardiac output of pregnancy superimposed on that of coarctation. This may aggravate a pre-existing strain or impose a new one. Although one may expect some lightening of this burden toward the end of pregnancy, the stress of labor may be too much for a thinned aorta or cerebral artery. Already defective valves may be further damaged.

The work of Goldblatt and others has indicated the role of the kidney and renal blood flow in the genesis of hypertension. Ryland and Steele have shown that decreased renal blood flow in coarctation of the aorta is the most likely cause of the associated hypertension. By clamping the aorta proximal to the renal arteries in dogs, Steele was able to produce

The first patient, R. P., a 26-year-old white primigravida, with a negative Wassermann and a funnel typical contracted pelvis, was first admitted in the fourth month of pregnancy for study of cardiac condition discovered at the initial clinic examination when signs of mild cardiac failure were noted. The past history was unremarkable except for dyspnea and palpitation on effort for six years. She had never suffered precordial pain or leg cramps. The patient showed some cyanosis and moderate dyspnea. There was marked evidence of collateral circulation. There was a soft blowing apical systolic murmur, and a loud harsh systolic murmur at the base. No diastolic murmurs were heard. Blood pressures RA 140/74, LA 130/80, not obtainable in the lower extremities. There was a marked temperature difference in the upper and low extremities. Chest film showed scalloping of the ribs and cardiac enlargement in the region of the left ventricle. The electrocardiogram showed normal sinus rhythm, rate 111, PR 0.16, QRS 0.07, no deviation of electrical axis, split QRS<sub>2</sub>, split R<sub>1</sub> and R<sub>2</sub>, T<sub>1</sub> and T<sub>2</sub> positive, and T<sub>3</sub> negative. Strayhorn has previously reported the case with detailed studies on cardiac function. As pregnancy progressed, the heart sounds became louder, the basal murmur louder, and the pulsations in the collateral vessels more pronounced. There was an increase in cardiac output out of proportion to the increase in oxygen consumption. The cardiac output fell just before term and returned to normal post partum. The patient was carried to term under strict regimen of limited activity and a classical cesarean section done under open drop ether with delivery of a 3,500 Gm. living infant. Sterilization was not performed. Palpation of the abdominal aorta during operation revealed the vessel to be of normal dimensions but only very feeble pulsations were felt. During operation the blood pressure dropped considerably but returned to former levels within a few hours. The section was done primarily because of fear of rupture of the aorta. Follow-up studies one month post partum revealed improvement in symptoms which had increased during the pregnancy. The physical signs were less marked. The electrocardiogram showed definite left axis deviation. Six months post partum there was no evidence of cardiac failure.

The second patient, E. B., a 23-year-old white primigravida, with a negative Kline reaction and normal pelvis, was admitted for study in the thirtieth week of gestation because of hypertension and history of known heart disease since the age of 5. She had had dyspnea on exertion for many years, recently aggravated by the pregnancy. There had never been precordial pain or leg cramps. Examination revealed the patient to be free of any distress. A systolic thrill was felt over the base. A loud systolic murmur was heard over the entire precordium, transmitted intensified along the course of the aorta down the back. There was no clinical evidence of collateral circulation. Blood pressures: RA 138/75, LA 135/70, RL 120/90, LL 115/90. On x-ray the heart was enlarged to the left. There was no notching of the ribs. The aortic knob was small. The electrocardiogram showed a tendency to left axis deviation. During the remainder of the pregnancy there was an increase in dyspnea and ease of fatigability. After a four-hour labor, the patient was delivered spontaneously of a 3,040 Gm. living infant. Renal function tests and blood chemistry during the puerperium were normal. Follow-up studies ten weeks post partum revealed that the patient tired very readily and felt unduly weak. She had no chills, fever, or precordial pain. For the first time a diastolic murmur was heard at the base transmitted down the left sternal border. Blood pressures RA 135/80, LA 130/60, RL 110/80, LL 100/80. There were no petechiae. Liver and spleen were not palpated. The development of the diastolic murmur suggested the following possibilities: damage to the aortic valve, stretching of the aortic ring, damage to the aortic wall, or formation of vegetations on the valve.

The third patient, R. Z., a 27-year-old Maltese primigravida, with normal pelvis and negative Kline reaction, was admitted for study of hypertension noted at initial clinic visit in the fourth month of pregnancy. Past history was entirely negative. Examination revealed evidence of collateral circulation, attenuation of the retinal arterioles, cardiac enlargement to the left, a harsh systolic murmur audible over the entire precordium and transmitted down the back over the course of the aorta. A bruit was heard over the pulsating vessels in the scapular region. Blood

## MENSTRUAL ENDOMETRIAL BIOPSY

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IT IS generally recognized that endometrial specimens can be obtained as a simple office procedure, without the need even for local anesthesia, and devoid of any practical risk, in all cases in which a thorough curettage is not necessary. Such specimens have become indispensable in the diagnosis of various types of menstrual difficulties and in sterility studies.

For these purposes one usually wishes to secure the specimen as near an expected menstrual period as possible, to note the evidence of corpus luteum activity, and if present, its degree. The secretory changes in the endometrium are a late interval occurrence, and probably continue to the beginning of menstruation. Consequently the nearer the onset of menstruation the specimen is obtained, the more accurately does the endometrium reflect the endocrine factors as they actually exist.

However, even in menstrual cycles which are considered to be "regular," there is usually a normal variation; thus the twenty-eight-day cycle may vary between twenty-six and thirty days, and sometimes more than this, in women who have no complaints. Ovulation time doubtless varies between certain limits in succeeding cycles in the same woman, also the interval between ovulation and the height of corpus luteum activity, and between this time and the beginning of menstruation.<sup>1</sup>

Because of these variations, one does not know, when the endometrium specimen is taken before menstruation begins, whether the maximum secretory changes have or have not taken place. That is, the specimen may be taken with the expectation that menstruation will begin within the next twenty-four hours, and had the endometrium not been traumatized by the procedure, that particular period might not have begun until forty-eight or seventy-two hours later. As a consequence, had such been the case, a specimen is obtained which does not show the changes which would have been seen had the specimen been taken later.

In consideration of these factors, we have been doing endometrial biopsies after menstruation has begun. We have found that nearly all the specimens which were obtained within the first three hours are satisfactory for histologic examination, and all taken within the first two hours have been satisfactory. Specimens taken after three hours may be unsatisfactory, since disintegration and desquamation may have proceeded to a point where the cellular structures are destroyed.

an increase in diastolic pressure in the femoral as well as the carotid artery. Pregnancy is known to increase the renal burden and may thereby aggravate the underlying condition.

### SUMMARY

Coarctation of the aorta is discussed and the literature surveyed with regard to pregnancy complicated by this condition. Three additional cases are analyzed. Evidence is presented to show that pregnancy adds to the risk in patients with this condition.

### CONCLUSIONS

Pregnancy and labor present definite risks to patients with coarctation of the aorta. Therefore contraception is indicated in this condition. In patients presenting themselves early in pregnancy, therapeutic abortion is definitely indicated. If pregnancy is far advanced and interruption from below not feasible, delivery should be effected by cesarean section and sterilization performed. In isolated instances it may be desirable to carry a patient a short time to viability of the infant with full knowledge of all the risks involved.

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Another important advantage of this method is that one does not inadvertently do an abortion, since one can never be certain that the next menstrual period will occur.<sup>2</sup> The only disadvantage is that it is not always feasible to obtain the specimen during this rather narrow range of time, and one must wait until the next period.

Biopsies done in the office on the menstruating uterus have not been followed by any undesirable consequences.



Fig. 3.—W., aged 25 years. Sterility study. Specimen taken about two hours after menstruation began. Changes shown are within normal limits, and the cellular structure is intact. The fact of ovulation and corpus luteum formation and activity is definite.

#### CONCLUSIONS

1. It is essential that endometrial specimens be taken as late in the menstrual interval as possible, to insure finding maximal endocrine changes.

2. Because of the variation in menstrual intervals, and because co-ception may have occurred following the preceding ovulation, it is advisable to secure the specimen after the onset of menstruation. This insures the maximal changes and permits more accurate diagnosis of endocrine factors, and obviates the chance of interrupting an early pregnancy.

3. Specimens obtained within two hours after the onset of menstruation are histologically intact.

4. There is no added risk in doing the biopsy at this time.

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The ideal time would be immediately after bleeding began, but this is not usually possible. One can always be certain, if the specimen is taken at this time, that all the changes have taken place which are going to take place.

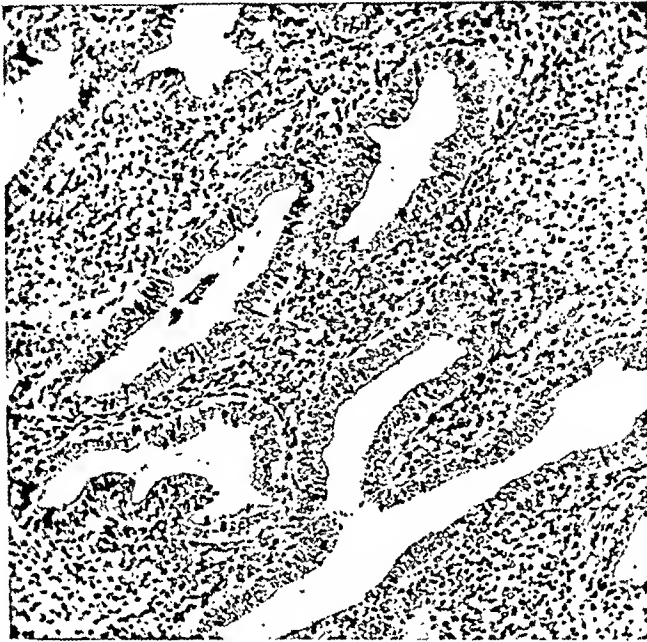


Fig. 1.—F. H., aged 18 years. Endocrine investigation in relation to epileptiform attacks. Patient was three days over her expected menstrual period, and was of the opinion that menstruation was imminent. Biopsy was done, but the period did not begin until four days later. Here is a specimen obviously deficient in the normal changes, but since the specimen was taken four days too soon, no conclusions can be drawn from it.

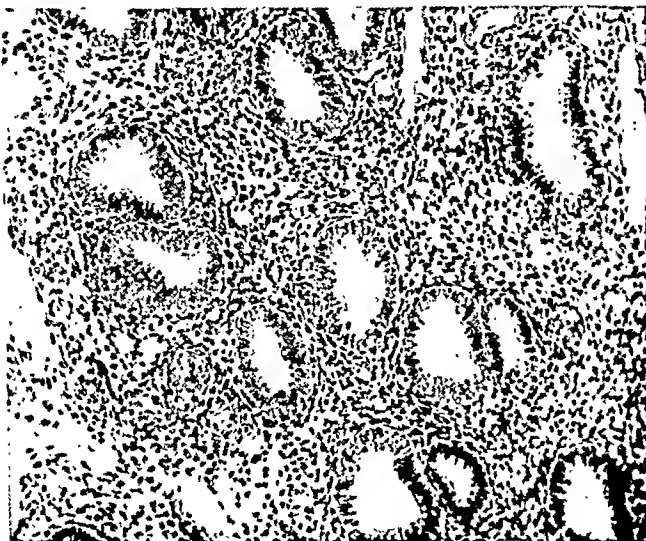


Fig. 2.—G. S., aged 37 years. Sterility study. This specimen is generally of the same pattern as shown in Fig. 1. However, it was taken within an hour after menstruation began. The cellular structure is intact. It shows a definite endocrine deficiency, particularly in that of progesterone. Since menstruation had already begun, the development is maximal, and the deficiency seen is actual.

shaped cells arranged in solid, moderately branching plexiform epithelial masses. There was generalized nuclear hyperchromatism and a moderate number of mitotic division figures. The tumor was more or less limited in its spread and did not invade beyond the lower level of the cervical glands. At the lower zone of the proliferating tumor nests, a rich lymphocytic infiltration was seen. *Sections of uterus* (Fig. 3) showed the endometrium to be poorly outlined and replaced in many areas by a wide, ill-staining necrotic layer bordered by dense zones of lymphocytes. Epithelioids and giant cells of the typical Langhan's type also were found in considerable number. In the deeper layers of the myometrium the lymphocytic infiltration was more pronounced. The tuberculous process extended to the ostia of the resected tubes. Ziehl-Neelsen stain of the endometrium was negative.

*Pathologic Diagnosis.*—Epidermoid carcinoma of the cervix, Grade II. Chronic ulcerative caseous tuberculosis of the body of the uterus with pyometra, and miliary tuberculosis of the uterine serosa.



Fig. 1.—Uterus, laid open, showing extensive tuberculous ulceration of the entire endometrium, and the carcinoma of the cervix (the latter marked by arrow). (X3.)

#### DISCUSSION

*Review of Literature and Frequency.*—The co-existence of cancer and tuberculosis in the uterus is extremely rare. Strachan,<sup>1</sup> in a review of this subject, states that he found only 8 such cases reported in 1924, 7 from Germany, and 1 from France. He added one case of his own, which, according to his statement, is the first of its kind ever to be reported in the English literature. In our review of the literature, which appears to be more thorough, but perhaps also not all-inclusive nor exhaustive, we found altogether 27 such cases reported, not counting those which were merely cited in statistical tables or reviews (such as Lubarsch's and

# THE COEXISTENCE OF CARCINOMA AND TUBERCULOSIS OF THE UTERUS

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THE simultaneous occurrence of tuberculosis and cancer in any organ is rare, and, in the uterus, is extremely rare. This fact alone, coupled with the interesting clinical and pathologic features that it presents, warrants a reporting of this case and a review of the literature.

## CASE REPORT

Mrs. S. M., a Syrian-Jewish married woman of 46 years, was admitted to the Israel Zion Hospital on Feb. 24, 1938, with the chief complaint of vaginal bleeding. Family history and past history were irrelevant. She was gravida iv and para i. A son, aged 33 years, was in good health. The menstrual cycle was  $14 \times 30 \times 6$ , with menopause at the age of 40. For four weeks before admission she had a profuse painless vaginal bleeding. She lost 14 pounds in weight within one year. Physical findings were essentially negative. She was fairly well nourished. Heart and lungs were negative. Uterus was soft, boggy, and retroverted. Cervix was eroded. Blood examination showed erythrocytes 4,000,000, leucocytes 8,000 per c.mm. with a normal differential. A preoperative diagnosis of retroversion, cervical polyp, and fibroid uterus was made. On Feb. 25, 1938 a total hysterectomy was done, leaving both adnexa which appeared normal. When tension sutures were introduced in the uterus during the operation, pus escaped along the suture lines. This was interpreted as being due to pyometra. The postoperative course was uneventful, and patient was discharged twenty-two days later. When seen, twenty-two months after the operation, the patient was apparently in good health. She had gained 20 pounds in weight and, as far as could be determined, she had no symptoms or signs referable to the lungs or pelvic organs. A roentgenologic examination of her lungs was essentially negative. She has also been followed up at the Memorial Hospital of New York, where no treatment was given her, as "at no time was any lesion found after the operation."

*Pathologic Findings.—Gross Appearance of Uterus:* Uterus was rather small, weighing 60 Gm. and measuring 70 mm. in length, from 25 to 30 mm. in width, and from 20 to 30 mm. in thickness. The fundus was rounded, globular, and fluctuant. On the posterior aspect in the midline, 2 cm. distal to the fundic rim, a subserous, pea-sized, calcified yellowish nodule was seen. On inserting a fine probe within the cervical cavity, the latter was found to end blindly at the internal os and no continuity between it and the uterine cavity could be established, except by a forceful thrust of the probe. The cervical canal was narrow, but free from exudate. The cavity was filled with a thick, stringy yellowish white purulent matter. The entire endometrium from the fundus and to the internal os presented a ragged, cupped out, honeycombed appearance (Fig. 1). On closer inspection, numerous pin-point-sized, yellowish tubercles could be seen scattered throughout the endometrial surface. The myometrium was thin, averaging 15 mm. in width. The ulceration ceased abruptly at the internal os.

*Cervix:* Portio vaginalis was smooth, pinkish, and glistening. At its junction with the cervical canal, there was a small, fairly circumscribed nodule, 8 mm. in diameter, which was slightly raised and its upper surface somewhat roughened (Fig. 1). On section, it showed slight thickening of the lining epithelium.

*Microscopic Findings.*—Section of the cervix, in the region of the grossly observed nodule, showed the surface to be mostly ulcerated and only partly lined by considerably hyperplastic epithelium which passed abruptly into a diffusely growing tumor (Fig. 2). This consisted mainly of masses of polyhedral or spindle-



TABLE I. SCHEMATIC TABULATION OF REPORTED CASES IN THE LITERATURE OF COMBINED CARCINOMA AND TUBERCULOSIS OF THE UTERUS AND CERVIX

AUTHOR AND YEAR	AGE	SYMPTOMS AND SIGNS			PATHOLOGIC LESION				
		MENORRHAGIA	METORRHAGIA	PAIN	CARCINOMA OF CERVIX	CARCINOMA OF ENDOMETRIUM	TUBERCULOSIS OF CERVIX	TUBERCULOSIS OF ENDOMETRIUM	TUBERCULOSIS OF MYOMETRIUM
Von Franque 1st case (1894)	43	*	*	*		+		+	
Von Franque 2nd case (1894)		*	*	*	+		+		
Von Franque 3rd case (1894)	40	*	*	*	+			+	
Von Reeklinghausen (1896)		*	*	*	+	+		+	
Bass (1899)	61	*	*	*	+			+	
Wallart (1903)	55	*	*	*	+	+		+	
Wallart (1903)	50	*	*	*	+		+		
Wallart (1903)	37	*	*	*	+			+	
Stein (1903)	48	*	*	*	+			+	
Schottlander (1905)		*	*	*	+		+		
De Josselin DeJong (1906)	64	*	*	*		+		+	
Eisenstein (1910)	24	*	*	*	+			+	
O'Halluin and Delval (1910)	35	*	*	*		+	+	+	
Schmidt (1914)	55	*	*	*	+		+		
Strachan (1924)	40	*	*	*	+			+	
Gais (1926)	47	+	+	*		+			+
Menniti (1933)	50	*	*	*		+		+	
Menniti (1933)	46	*	*	†	+		+		
Kris (1933)	45	+	*	†		+		+	
Votta (1934)	53	*	†	†		†		†	
Soler (1934)	63	*	†	†		†		†	
Soler (1934)	40	†	*	*	†			†	
Tommaseil (1935)	37	† + †	*	*		†	†		
Schultze		*	*	*	+			†	
Monckeberg		*	*	*	squamous	adeno		†	
Ravid and Scharfman (1939)	50	†	†	*	+			†	

\*Not mentioned.

Tuberculosis of the cervix is mostly a secondary infection. Altogether about 300 such cases have been reported in the literature,<sup>10</sup> of which only 35 were found to be primary.

Carcinoma of the cervix occurs at a frequency of 90 per cent, that of the fundus 8 per cent, and of the endocervix 2 per cent of all uterine malignancies.

*Clinical Picture.*—There are no specific symptoms or signs characteristic of co-existent tuberculosis and cancer of the uterus. In fact, as seen from the review of the literature (Table I), in none of the cases were there any pathognomonic signs, the diagnosis having been made only during or after the operation by the surgeon or by the pathologist.

Certain signs and symptoms, however, when present, may be helpful in recognizing the coexistence of both of these lesions.

The most common complaint is menstrual irregularity, usually in the form of metrorrhagia. Pain appears to be almost constantly present, and is characterized usually as an aching sensation in the pelvic region, the back or in either lower quadrant, with occasional radiation to the thigh or vertebra. Occasionally, an

Ferroni's). It would appear that the only case reported in the American literature is that of Gais.<sup>2</sup>

At this point, it should be mentioned that a rigid criterion is to be applied in accepting such cases, so that only those in which both carcinoma and tuberculosis were proved beyond doubt are to be included in this review. Thus, cases of a "carcinomatous degeneration of a fibroid"(!)<sup>3</sup> and the like, which are cited in the literature as instances of association with tuberculosis of the endometrium, cannot, for obvious reasons, be accepted in this collected series.

No mention is made of such cases by Kaufman,<sup>4</sup> although he states that "in rare cases the combination of cancer and tuberculosis is seen." Lubarsch,<sup>5</sup> however, found 29 cases of cancer-tuberculosis combination in 129 cancers of the uterus, or 22.5 per cent. Imamura<sup>6</sup> found 8 such combinations among 3,103 patients with carcinoma of uterus, or in 0.25 per cent of all cases of cancer of the uterus. Similar cases of combined tuberculosis and cancer have been described by a number of observers in other organs, such as in the central nervous system, gastrointestinal tract, breast, skin, lungs, kidney, urinary bladder, penis, face, lips, tongue, larynx, and other organs.



Fig. 2.



Fig. 3.

Fig. 2.—Low power photomicrograph of cervix ( $\times 100$ ), showing an epidermoid carcinoma, Grade II, plexiform in structure, growth being limited to the lower level of the cervical glands.

Fig. 3.—Photomicrograph of uterus, showing extensive caseation-necrosis of most of the endometrium on the left, lymphocytic and epithelioid zones on the right and many Langhan's giant cells scattered throughout. Three normal glands are seen in the upper right ( $\times 28$ ).

Tuberculosis of the female genital tract by itself is rather infrequent. According to King<sup>7</sup> and Greenberg,<sup>8</sup> pelvic tuberculosis occurs at the frequency of 1 to 8 per cent of all pelvic inflammations. In the tuberculous institutions, according to the statistics of Stopper and Posner,<sup>9</sup> the incidence is 20 to 30 per cent. At the Israel Zion Hospital, a general hospital which is representative of a cross section of a metropolitan American community, tuberculosis of the female genital tract was encountered 8 times in 22,000 surgical specimens within ten years, giving it a percentage of 0.03 per cent, and only 2 times in the past four years in 2,000 operative gynecologic cases, an incidence of 0.1 per cent of all gynecologic conditions.

nancy this increased demand is probably due to the presence of the fetus in utero. If the organ is unable to meet this demand by hypertrophy and hyperplasia, a state of deficiency or decompensation develops. One of the manifestations of thyroid deficiency is, of course, obesity.

Patterson, Hunt, and Nicodemus<sup>2</sup> demonstrated that in subclinical hypothyroidism during pregnancy the mother absorbs thyroxin from the fetus, producing fetal hypothyroidism. The fetal thyroid then reacts to this drain by undergoing extreme hyperplasia and hypertrophy. This leads to permanent damage to the gland with subsequent clinical thyroid disease later in life, dependent, of course, upon iodine supply and physiologic demands. Anselmino and Hoffman<sup>3</sup> reported a marked increase in the amount of thyroid hormone in the circulating blood of the mother during pregnancy; the amount increases as gestation progresses. The average amount of thyroxin found in the blood during pregnancy is twenty units to the cubic centimeter, according to these observers. Soule<sup>4</sup> substantiated the findings of Anselmino and Hoffman and expressed the belief that the increase in thyroid hormone is due to an actual physiologic hyperfunction of the thyroid gland during pregnancy. Williams<sup>1</sup> believes that thyroid deficiency results in a defective germ plasma and premature termination of pregnancy; if pregnancy continues, monstrosities result. Breckenridge<sup>5</sup> reports abortion, premature labor, and fetal death caused by thyroid insufficiency; his report includes 25 cases in which there was complete relief following thyroid medication.

With the foregoing evidence as a foundation, a series of cases was started, based upon the thesis that fetal obesity is due to a fetal thyroid deficiency which can be corrected by placing a sufficient saturation of thyroid extract in the fetal blood stream. One hundred and sixteen women have been given thyroid extract orally during four or more months of their pregnancies. Patients receiving less than four months of continuous treatment have not been included in this series. Each patient received not less than 3 gr. (0.2 gm.) and not more than 6 gr. (0.4 gm.) daily. Armour's enteric coated 1 gr. (0.065 gm.) tablets were used on all cases. These patients received no other medication that could influence weight and they were told to eat a normal, well-balanced diet without qualitative or quantitative food restriction. They were given no extradietary calcium or vitamins.

These women were seen at intervals of not less than two weeks at which time routine prenatal care was given; in addition, they were carefully examined for evidence of hyperthyroidism. The fact that these signs failed to develop in a single case is significant and further proves clinically that there is a thyroid deficiency during pregnancy; if 116 normal, nonpregnant women would be given from 3 to 6 gr. (0.2 to 0.4 gm.) of potent thyroid extract daily over a period of four or more months many of them would develop signs of hyperthyroidism.

Brown<sup>6, 7</sup> made two very comprehensive reports on the administration of thyroid extract during pregnancy; he was one of the first workers to discover the extreme variability of potency of the various thyroid preparations on the market. Davis<sup>8</sup> agrees with Brown; he advises selecting a single product of known high potency and giving it continuously to all patients throughout pregnancy. He further advises beginning the administration of thyroid extract prior to the pregnancy to avoid abortions and fetal maldevelopments. Mussey and Haines<sup>9</sup> advise giving a standard

afternoon rise in temperature is noted. There may also be nervousness and irritability. It is to be emphasized, however, that the general systemic signs of tuberculosis are prominent by their absence. The patient is usually pale, sallow complexioned, and her anemia is not accountable for by the loss of blood through the menstrual disturbance, but could be attributed to the systemic tuberculosis infection. Pelvic examination usually reveals no suspicion of tuberculosis, and often is negative for malignancy as well. The entire physical examination is very often essentially negative.

#### PATHOGENESIS

*Tuberculosis of the Female Genitalia.*—This is mainly confined to the tubes and endometrium. Rarely, it may also involve the vulva, vagina, or the cervix.

It is the accepted view today that tuberculosis of female genitalia is mainly a secondary infection, with the primary focus being located elsewhere in the body, but chiefly in the lymph nodes or in the abdominal organs. The infection is usually a descending one, namely, from the tubes to the endometrium. This is borne out by the fact that, according to all statistics, the tube is involved in almost 100 per cent of the cases of pelvic tuberculosis, while the endometrium is affected only in 40 per cent. The mode of origin of tuberculosis of the cervix, when not associated with an obvious primary focus elsewhere, can be explained as being embolic in nature. For, as shown by the experimental work of Korper and Vidal,<sup>11</sup> it would appear that when tubercle bacilli gain entrance into the blood stream they disappear quickly from it and may lodge as emboli in various locations.

The infrequency of tuberculous involvement of the uterus, itself, as explained by some, is supposed to be due to the continuous cyclic physiologic activity of the endometrium with its periodic desquamation, which makes bacterial growth rather unfavorable. This, however, is rather doubtful, because no complete or even partial desquamation of the endometrium takes place in normal menstruation. Other factors, however, such as trauma, antecedent infection and other pathologic changes which interfere with the menstrual cycle, may, in some measure, favor the development of tuberculosis.

Tuberculous involvement of the endometrium may take place either via the blood stream, through a lymphatic spread from the tube, in association with tuberculosis of both tubes and ovaries, as a secondary spread from the lungs, bronchial or mesenteric lymph nodes, or, rarely, in generalized miliary tuberculosis. More rarely it may occur as an ascending infection via the lymphatics in cases of tuberculosis of the vagina or vulva.

It is noteworthy that, contrary to what may be expected, pulmonary tuberculosis, at least in its active form, is rather infrequently associated with pelvic tuberculosis. In only about 25 per cent of cases of pelvic tuberculosis were the lungs also involved.<sup>12</sup> But as in the majority of pulmonary tuberculosis, the hilar lymph nodes are also involved, these most likely form the source of uterine tuberculosis. Other lymph nodes, especially the mesenterics, are likewise a possible source of the infection.

#### ASSOCIATION OF CANCER AND TUBERCULOSIS

For the last one hundred years there has been waging a lively controversy as to whether tuberculosis and cancer can coexist in the same organ or not. Rokitsky,<sup>13</sup> in 1855, was the first to expound the view that there is a definite antagonism between the two, meaning that tuberculosis and cancer cannot be present in the same organ. However, under the influence of Votta's work,<sup>14</sup> and through his own further experiences, he later changed his previous generally accepted view and admitted that carcinoma and tuberculosis can coexist, but that this occurrence was rather rare.

The coincidence of tuberculosis and carcinoma, as first suggested by Lubarsch in 1888,<sup>5</sup> and widely quoted since, may be viewed as occurring in one of the following ways: (1) As a purely accidental occurrence, either disease having no influence one on the other. (2) Metastatic carcinoma may be found growing near an old tuberculous lesion or a fresh miliary tuberculous eruption, especially in a serosal spread. The cancerous cachexia, then, offers a good nutritional basis for

the dormant tubercle bacilli. (3) A fresh tuberculous infection becoming engrafted on a fully developed carcinoma. (4) Carcinoma is superimposed on a chronic progressive tuberculosis, which serves as a predisposing factor. (5) A hypothetical simultaneous occurrence of both cancerous and tuberculous processes.

Pettinari,<sup>15</sup> in his work "The Antagonism of Malignant Tumors and Tuberculosis," came to the conclusion that there exists no local or general antagonism between the two. He found that there was no attenuation of the virulence of the tuberculous process in the presence of the tumor, nor were the invasive properties of the tumor in any way diminished when in direct contact with the tuberculous lesion. The latter, in fact, was replaced by the tumor. Others, like Aschoff,<sup>16</sup> Wallart,<sup>17</sup> Stein,<sup>18</sup> and Von Franque,<sup>19</sup> believe that in some cases tuberculosis even predisposes the growth of cancer. The problem of the so-called antagonism between tuberculosis and carcinoma formed the subject of a much heated controversy at the "Congress of the Italian League of Fight Against Cancer" in 1932, and found in Centanni its most fervent protagonist. However, no definite conclusions were arrived at in this Congress.

In experiments on animals, Ayellow,<sup>20</sup> in 1932, came to the conclusion that there is no antagonism between the two diseases. He also noticed that tuberculosis aggravates cancer, and in splenectomized animals there was an increase in the frequency of development of cancer as well as in the co-existence of cancer and tuberculosis. On the other hand, Centanni,<sup>21</sup> in his experiments on mice, found that living tubercle bacilli inhibited the growth of implanted cancer.

As to the problematical question which comes first, it would seem, from perusal of the literature, as well as from our own case, that it is usually tuberculosis which precedes cancer. The tuberculous involvement of the endometrium in our case was of long duration, as evidenced by the extensive caseation which resulted in pyometra. On the other hand, the carcinomatous involvement of the cervix in this case was definitely of a relatively more recent occurrence.

#### PATHOLOGY

The gross and microscopic features vary according to the type and location of the tuberculous and cancerous lesions. Tuberculosis of the cervix may occur in either of the following forms: (1) Miliary, (2) ulcerative, (3) vegetative (papillomatous), or (4) hyperplastic.

The ulcerative form may be difficult to distinguish grossly from carcinoma. Tuberculosis of the uterus, as mentioned previously, is usually confined to the endometrium and is secondary to a lesion in the adnexa or pelvic peritoneum. It occurs mostly as a diffuse interstitial and ulcero-caseous form with pyometra. Rarely does it assume a disseminated miliary form. The infection, as a rule, is limited to the endometrium and in only a very small percentage of the cases it may spread through the myometrium and involve even the serosa. Occasionally, as seen in our case, calcified tuberculous foci may be found over the uterine serosa.

In the early stages of uterine tuberculosis, there may be extensive metaplasia of the glandular epithelium in the surface layer. Histologically, the typical tuberculous granulation tissue or discrete tubercle formation is the usual characteristic picture found. Diffuse necrosis and caseation may, however, also be seen. When the internal os is closed, as in our case, the uterine cavity becomes distended, fluctuant, may reach a considerable size, with secondary pressure atrophy of the wall, a typical pyometra.

Carcinoma of the uterus, in association with tuberculosis, may occur in any of the usual anatomic forms known. The gross and microscopic appearance of carcinoma of the cervix and fundus are well known today, and, as they form no special feature of this paper, will not be discussed here. Suffice it to say, that there are no fundamental differences in the gross and microscopic features of carcinoma of the cervix and uterus when occurring alone or when in association with tuberculosis.

#### DIAGNOSIS

The diagnosis of the coexistence of tuberculosis and cancer of the uterus, as pointed out before, is very difficult or well-nigh impossible. As a matter of fact, in none of the cases reported, not excluding our own case, was a preoperative

diagnosis made. This may be explained by the fact that the possibility of the association of the two conditions is not generally recognized, as well as because there are no pathognomonic signs that would lead one to suspect the coexistence of the two lesions. The patient usually presents herself for signs and symptoms relative to malignancy. If, however, at the same time she shows undue cachexia or debility, which is out of proportion with what is usually found in early uterine carcinoma, the possibility of the coexistence of tuberculosis should always be kept in mind. Diagnostic curettage performed in such a case should not rest with the finding of malignancy alone, but should also be supplemented by bacteriologic study of the curettings.

In the microscopic diagnosis of these two conditions two points must be kept in mind: (1) Occasionally atypically appearing epithelial hyperplasia may be seen in the neighborhood of a tuberculous focus, and (2) occasionally, as pointed out by Ribbert<sup>22</sup> and Kermauer and Schottländer,<sup>23</sup> foreign body giant cells in the vicinity of a breaking down cancer may resemble and be mistaken for Langhan's giant cells. In tuberculosis, however, the typical histologic picture, and especially the finding of tubercle bacilli on smear or in the tissue, makes the diagnosis absolute. In the final differential diagnosis the rarer forms, such as nonspecific chronic endometritis and syphilitic endometritis, have also to be kept in mind. Animal inoculation and serologic studies will help in the final diagnosis.

#### SUMMARY AND CONCLUSIONS

1. A case of coexistent tuberculosis of the endometrium and carcinoma of the cervix is reported and a review of similar cases in the literature is given.

2. The pathogenesis and mode of spread of tuberculous infection of the female genital tract is discussed.

3. There are no authentic proofs to support the view of the existence of the so-called antagonism between tuberculosis and cancer in the same organ.

4. It would appear that tuberculosis usually precedes cancer when the two are associated in one organ. This association may be explained as a chance occurrence or by a predisposition of the tuberculous organ to the development of carcinoma.

5. No definite pathognomonic signs and symptoms exist for the association of the two lesions. However, undue anemia and debility, which are unaccountable by the usual metrorrhagia in cancer of the uterus or cervix, should be suggestive of the combined diagnosis of tuberculosis and carcinoma.

6. The therapeutic procedure to be adopted varies in accordance with the location and extent of each lesion and must be individualized for each case.

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## AN APPRAISAL OF THE ROUTINE USE OF SPECIAL POST-PARTUM EXERCISE\*

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WHAT is the value of the routine use of printed directions given to patients, which detail the kangaroo walk, knee chest, and other postures and exercises commonly recommended to minimize posterior displacements of the uterus in the post-partum period? How many patients with a retroposed organ in the early ante-partum period will maintain such malposition during and after the puerperium? Is such a condition influenced by special exercises or postural treatments? If so, to what extent? Is the incidence of retrodisplacements greater among primiparous or multiparous patients?

My purpose in presenting this subject is to offer some additional information on these and other rather controversial problems relating to uterine displacements. I shall not speak of the pathologic importance, the sequelae, the etiology, or the correction of such disorders by surgical or mechanical supports.

The material for this presentation has been collected by a long painstaking study of more than two thousand ante- and post-partum records of my private patients.

In this discussion a uterus is considered as retrodisplaced, when its long axis deviates posteriorly to the axis of the plane of the inlet. I have not classified the various degrees of misplacement nor have I tabulated retroflexion alone or retroversion alone, or both concomitantly.

At the expense of being a bit elementary and for clarity's sake, I might add that all pelvic examinations were made directly after the bladder was emptied. Further it must be remembered that the uterus is a mobile organ with a normal range of movement of almost 120 degrees. My findings, therefore, are merely relative in character.

The 2,150 records were examined, 228 of which could not be included because of the lack of sufficient detail. In this study the records are divided into two groups according to whether they had or had not received the exercise sheet in the early post-partum period. This sheet has on one side these words:

### INSTRUCTIONS FOR MRS.-----

Four days after your baby is born, you should begin to strengthen your muscles that have been so stretched while carrying and giving birth to your baby. Every morning and night lie flat on your back without a pillow with your hands

\*Presented at the Northeastern New York Obstetrical Society, May 15, 1939, and at the Medical Society of the County of Rensselaer, October 10, 1939.

beside your hips. Then raise your hips off the bed, at the same time draw up on your rectum as though you were trying to hold a bowel movement. Then replace your hips on the bed. Repeat this up and down movement, gradually increasing the number of times each day from five to forty, if possible.

These exercises will help you to regain your natural form, whereas inactivity with tight binders restricts movements and tends to keep the muscles soft and flabby. From the fifth day until four weeks after the baby's birth, you should not lie on your back any more than is absolutely necessary. This will help to prevent backward misplacements of your womb. Resting on the abdomen awhile each day is desirable and when up and about, walking around on your hands and feet for five minutes each morning is very helpful to prevent misplacements, especially when followed by a rest in the knee chest position as illustrated on the reverse side of this sheet.

You should report to me any bright red vaginal discharge that lasts longer than two days after leaving the hospital. Also phone for an appointment any time after the final examination (marked at the end of this sheet) if any vaginal discharge or other female trouble appears between your regular menstrual periods.

It is inadvisable for you to walk up and down stairs before the third week and only once a day during the third week after the birth. Your regular household duties must not be resumed until after the date listed below.

On the reverse side of the sheet, I have tried to picture to the patient the proper knee chest posture.

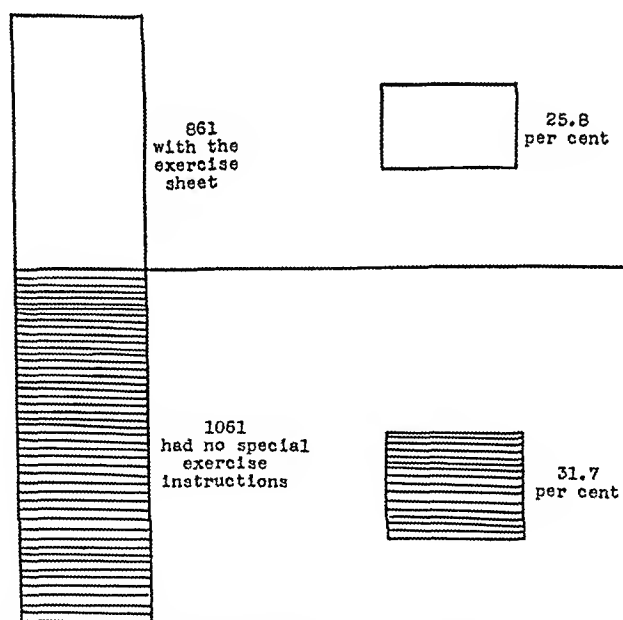


FIG. 1.—Showing post-partum deviations of the uterus in 1,922 patients, with and without exercise instructions.

#### MATERIAL OF THE STUDY

Fig. 1 shows 1,061 patients, illustrated by the shaded area, who had little other than occasional instructions, irregularly given by the nurse, to lie on the abdomen or to take the kangaroo walk. No printed or other illustrative detail was given to this group.

Of these, 31.7 per cent had retrodeviations at the sixth week's visit, whereas, there were 25.8 per cent posterior positions among the total of 861 patients who were given the exercise sheet. In other words, the tendency for displacements appears to be reduced 5.9 per cent among the exercise group.



Fig. 2 shows a study of 416 primiparous patients who had the results of a bimanual examination recorded before the end of the third month of pregnancy, as well as at the sixth-week post-partum visit. Two hundred and twenty-five patients were given the sheet and 191 were without it.

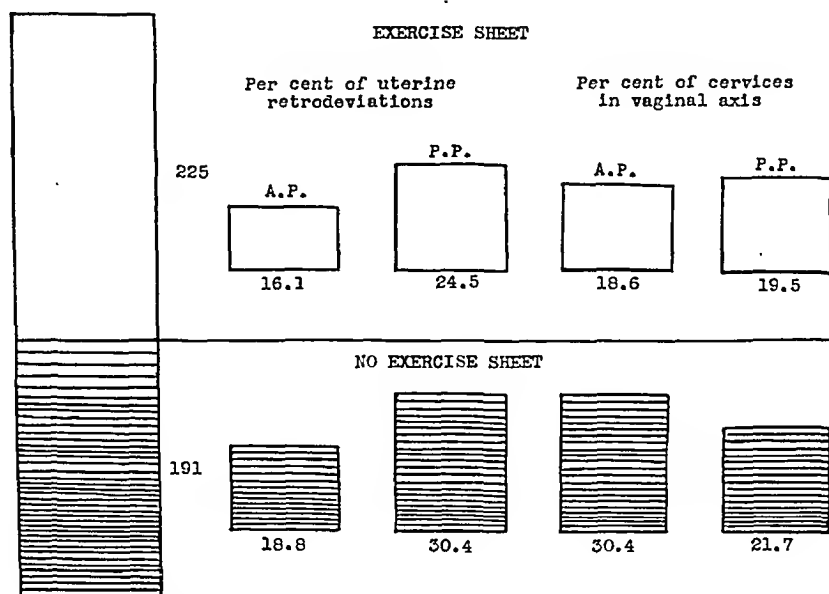


Fig. 2.—Showing results in 416 primiparous patients.

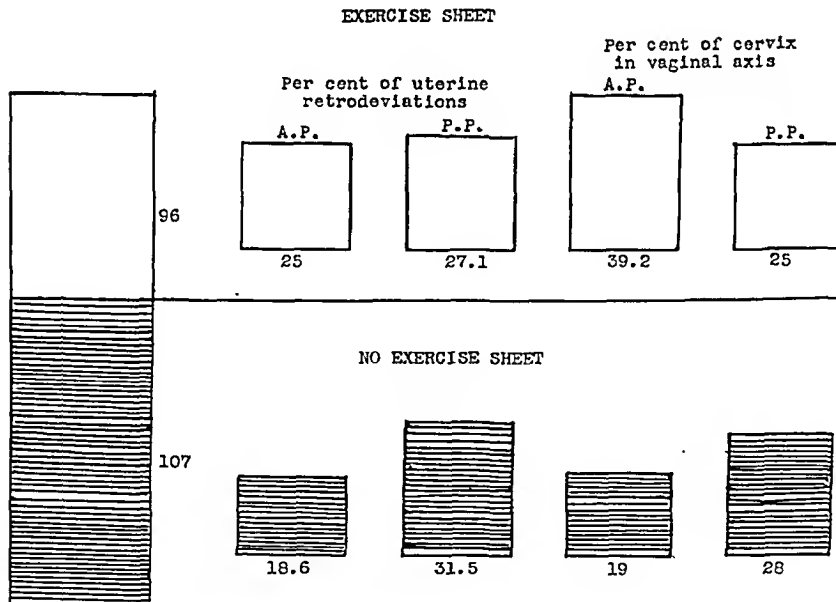


Fig. 3.—Showing results in 203 multiparous patients.

There are 16.1 per cent ante-partum uterine deviations in the exercise group and 18.8 per cent in the non-exercise group. At the sixth-week examination, this ratio stood at 24.5 per cent and 30.4 per cent, respectively. This tends to show two things: First, that there is an increase in the percentage of displacements in the post-partum over the ante-partum displacements in both groups. Second, that among the patients who did not receive the exercise sheet, 5.9 per cent more displacements occurred.

Fig. 2 shows the percentage of patients having the cervical canal in the vaginal axis. It is best studied with Fig. 3. It may be noted that in both primiparous and multiparous women, the incidence of cervixes in the vaginal axis, when compared with retroversions of the uterus, is higher in the ante-partum and lower in the post-partum group, or just the reverse of what happens to the uterus. I do not think that this has much bearing on our main subject but thought it worthy of observation as long as the data were available. It does show the unreliability of judging the position of the uterus merely by feeling of the direction of the cervical canal.

Fig. 3 presents similar statistical data on multiparous cases. Owing to the fact that such women are more prone to put off the time of coming to their doctor, and due to the lack of records showing the exact position of the uterus at the beginning of pregnancy, I found a total of only 203 records of this classification. Ninety-six patients were given the exercise sheet. They are represented by the clear upper portion. One hundred and seven had no exercise sheet. They are listed in the lower part of the oblong. Here we see that, regardless of less ante-partum retrodeviations among the patients who did not receive the sheet, nevertheless, those patients had 4.4 per cent more post-partum deviations of the uterus than those who were given the exercises.

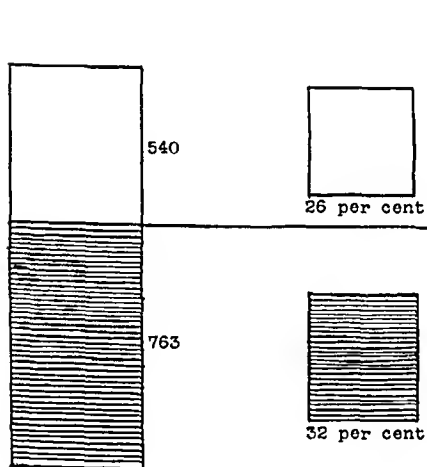


Fig. 4.

Fig. 4.—Showing post-partum findings in 1,303 patients in whom no ante-partum records were available. A 6 per cent decrease of retrodeviations occurs in the exercise group.

Fig. 5.—Showing normal increase of uterine displacements from ante to post partum in both groups (exercise and non-exercise).

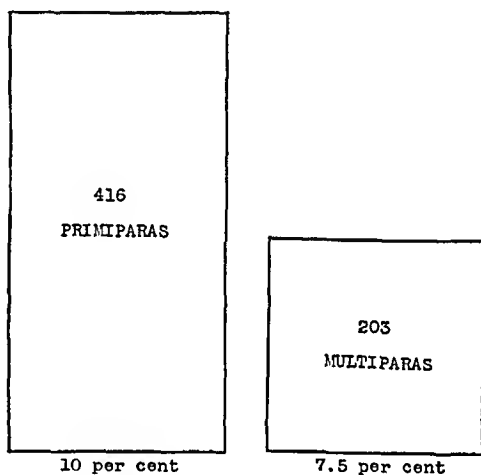


Fig. 5.

The multiparous cervix shows the same tendency as the primiparous cervix; namely, in the ante-partum cases, a relatively greater number of cervixes are in the vaginal axis than there are deflected uteri. In the post-partum cases, on the other hand, there are fewer cervixes in the vaginal axis than there are uteri that are retrodeviated. This tendency is a variable consonate, and I do not think that much attention should be paid to it. It is possibly caused by stretching or tearing of an unusually short pubocervical fascia during labor.

Fig. 4 shows the record of 1,303 patients whose case histories contained no ante-partum pelvic findings, but the post-partum detail was complete. It will be noted in the shaded portion, that there are more in the non-exercise group than in the exercise group and that there were 6 per cent more retrouterine deviations in the non-exercise group.

Fig. 5 shows an incidental finding in this study which, I believe, has further bearing on our subject. There is a constant average increase of post-partum retrodeviations over the ante-partum deviations of the uterus, amounting to 8.7 per cent. This is 10 per cent among 416 primiparas and 7.5 per cent among 203 multiparas. As I have already pointed out, this increase is most marked among the non-exercise group.

Fig. 6 gives a summary of the value of special exercises among a total of 610 patients whose ante- and post-partum records were complete. In other words, they were examined sufficiently early in the ante-partum period to record the evident nonpregnant position of the uterus. Also a detailed record of their post-partum examination was available.

Here, too, the benefit of the exercise appears to be fixed at nearly the same figure as that obtained by the previous studies, namely, 7 per cent.

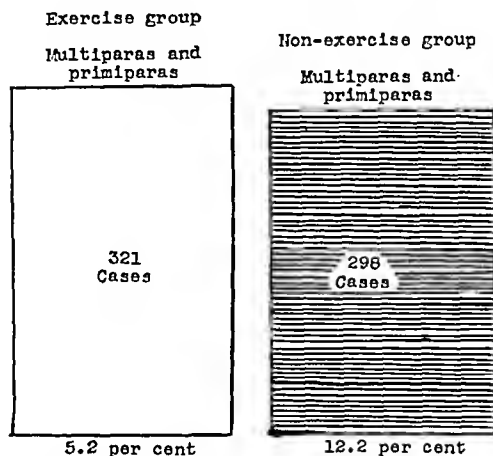


Fig. 6.—Showing comparative increase of uterine displacements from ante to post partum.

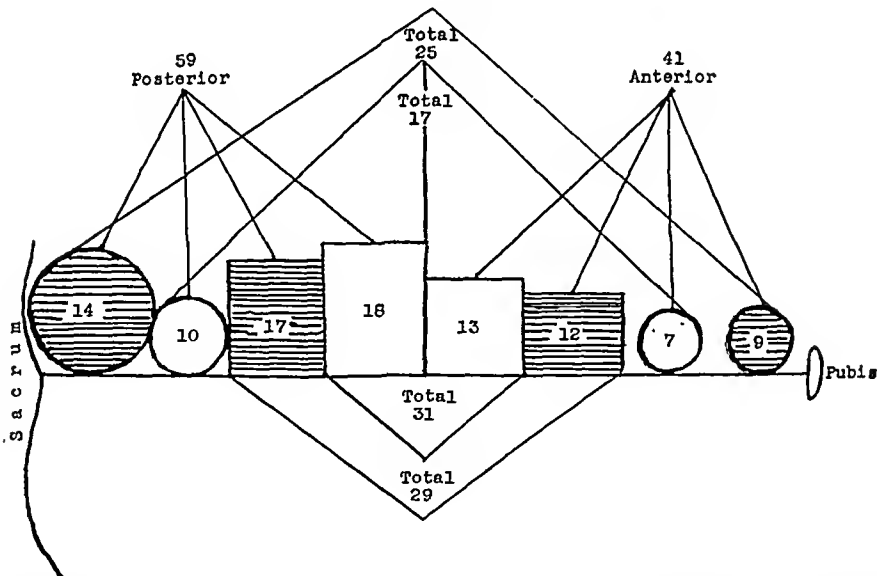


Fig. 7.—Showing post-partum findings in 100 cases of retrodeviations noted before the third month of pregnancy. Squares, primiparas; circles, multiparas; shaded area, no exercise; not shaded areas, with exercise.

Fig. 7 represents the records of 100 patients, all of whom were examined before the end of the third month of pregnancy and found to have a retrodeviation of the uterus.

Forty-one per cent of 100 known cases of ante-partum displacements are found to be normal positions at the six weeks' examination. Perhaps this is one of the factors that lead some women to say that they feel much better since having their baby. It may also be responsible for the abolition of some cases of dysmenorrhea.

It is my custom to make a routine pelvic examination of all nonmorbid puerperas on the seventh day. From this examination I am convinced that uterine involution is definitely enhanced among the patients who really do their exercises. I have noticed that leg strength comes back quicker in that group. It is possible that the routine use of such sheets minimizes the occurrence of embolism. I have not yet lost a patient from that cause.

Reports of this character, on the value of post-partum exercises, appear rather infrequently in the literature and show widely different conclusions. This may be due to personal interpretations as well as a disparity of accurate records.

Findley states that 20 per cent of the primipara and 25 per cent of the multipara-deviations are corrected by the knee chest and special exercise. Perhaps his patients are driven harder to their task than mine.

Schauffler, reporting on the use of the knee chest and special exercises in the puerperium of 169 patients, states that in the exercise group there were a total of 47.2 per cent misplacements, whereas in the non-exercise group there were only 34.5 per cent misplacements.

Lynch's excellent study of 1,230 cases showed 41.1 per cent of the entire series were displaced at some time during the first year following confinement. His figures show a wide discrepancy between private (19.6 per cent) and clinic (44.8 per cent) patients. I wonder if his patients were all examined by the same physician as was the case with these in this article.

#### SUMMARY

An analytical study of the uteri of 1,922 private obstetric patients is herein recorded; 861 were given special post-partum exercises. There were 1,061 controls. There was a decrease in the incidence of retro-deviations of the uterus, amounting to 5.9 per cent among the patients who were given the exercise sheet. This decrease varies but slightly among primiparas or multiparas. Of 100 known cases of retroverted uteri at the onset of pregnancy, 41 patients have been found normal at the sixth week post partum. The other 59 were still retrodeviated.

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Nicholas and Bray: Urological Problems as Seen by the Gynecologist, Urol. & Cutan. Rev. 43: 583, 1939.

There exists a close anatomic and embryologic relationship between the reproductive and urinary tracts. The symptoms may be primarily due to one tract, or secondary to pathology of the other. Chronic cervicitis, prolapse, and pelvic tumors are often the exciting cause of urinary tract pathology. Pathology of the urethra or ureter may simulate gynecologic symptoms. Hence, complete urologic studies are indicated in doubtful cases or before major surgery. The two systems must be carefully considered in arriving at a diagnosis and the coordination of findings by the gynecologist and urologist will be most helpful.

J. P. GREENHILL.

# THE ANAEROBIC STREPTOCOCCI IN TUBO-OVARIAN ABSCESS

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THE chronicity of tubo-ovarian abscesses is an old problem. In the 25 consecutive cases of this study, positive bacterial cultures were obtained from the pus in 23, contrary to the usually accepted idea that such pus is sterile. The anaerobic streptococcus was by far the most frequently encountered organism, being found in pure or mixed culture in 22 of the 23 positive cultures.

These 25 patients with chronic tubo-ovarian abscess were operated upon by the gynecological staff of the Henry Ford Hospital during the last half of the year 1937 and first half of the year 1938. Nineteen of the patients were white and 6 were colored. The average age of the group was 35.5 years, the oldest being 52 and the youngest 24. Seventeen were married, 3 single, 2 widowed, 1 separated, and 2 divorced.

The majority of the patients presented a history of recurrent attacks of lower abdominal pain and backache extending over a period of time varying from six months to fourteen years. The average duration was 25.3 months. The nature of the origin of these abscesses was obscure. Six of the patients gave definite history of previous gonorrhea and 6 admitted one or more previous abortions.

The average preoperative temperature was 99.2° F.; 10 had normal and 15 had elevations of temperature, the highest being 102° F. The white blood count was within normal limits in 8 cases and elevated in 17, the highest being 16,500.

All of the patients in this series were operated upon. In 22 cases the abscess was removed through an abdominal incision. Of the remaining three, two had a posterior colpotomy, and the other a posterior colpotomy followed by abdominal incision and drainage. Two of these patients died, one with symptoms of a terminal meningitis, and the other of acute postoperative peritonitis.

Specimens of the tubes and ovaries were examined in the department of pathology of the Henry Ford Hospital. In each instance a microscopic diagnosis confirmed the gross of chronic inflammation.

The pus obtained from the abscesses at the operating table was immediately inoculated (within five minutes) upon blood agar glucose slants and brain broth. Cultivation was done under aerobic, anaerobic, and partial (CO<sub>2</sub>) tension for a period of at least ten days. One of the two negative cultures resulted when a period of time of two and one-half hours elapsed between operation and implantation of the pus on artificial media. Subcultures were made for study and identification of the various organisms.

The aerobic bacteriologic findings in the 25 patients appear in Table I and the anaerobic in Table II.

Some form of the streptococcus was isolated by anaerobic methods in 22 of the 25 cases. The majority were obligate anaerobes, but 7 species, after subcultivation,

TABLE I. SHOWING INCIDENCE OF AEROBIC BACTERIA

ORGANISM	NO. OF CASES
1. Nonhemolytic streptococcus	3
2. <i>B. coli</i>	2
3. Staphylococci	2
4. <i>B. pseudodiphtheriae</i>	2
5. Hemolytic streptococcus	1
6. Gonococcus	1
7. Negative cultures	17

brand of desiccated thyroid in doses of about 4 gr. (0.24 gm.) daily for three or four days and then dropping to a maintenance dose of 1 to 2 gr. (0.065 to 0.12 gm.) daily.

Basal rates were done on the first 56 cases; the average rate of this group at an average time of four months' gestation was plus 2 per cent; the average rate after three months of treatment was plus 22 per cent. Basal rates were discontinued when it was discovered that an elevated rate is normal during the latter half of pregnancy.

Williams<sup>1</sup> states that there is a definite elevation in the basal metabolic rate during the latter half of pregnancy, due to the presence of the fetus in utero. It returns to normal about the tenth post-partum day. Sandiford and Wheeler<sup>10</sup> found that the state of pregnancy demands increased secretion of thyroid extract because of the presence of an increasing mass of active protoplasmic tissue, consisting largely of the fetal tissues and partly of an increase in maternal structures incident to pregnancy. They found no change in the basal rate in the early months of pregnancy, but found a distinct rise to plus 20 or plus 25 per cent in the final trimester. Mussey, Plummer, and Boothby<sup>11</sup> found that basal rates of plus 25 to plus 30 per cent during the latter half of pregnancy do not necessarily indicate the presence of hyperthyroidism. Davis<sup>8</sup> pointed out the fact that basal rates in pregnancy are confusing and fail to give a true picture of thyroid function. He believes that a clinical test with the administration of desiccated thyroid is the only method which can be accepted at present. From the foregoing evidence it was concluded that thyroid deficiency can exist during pregnancy despite the presence of a normal basal rate.

The average maternal weight gain during entire pregnancy in this group of 116 cases was 18.2 pounds (8.3 kilograms). The average fetal birth weight was 6.8 pounds (3,090 gm.). There was no fetal mortality or prematurity and no maternal mortality. These weights are not spectacular but they are fairly satisfactory since there were no qualitative or quantitative food restrictions. The most gratifying point in this series is the fact that no baby weighed more than 7 pounds 12 ounces (3,522 gm.) and none less than 5 pounds 11 ounces (2,590 gm.).

Because of the small size of these babies and the fact that no more than 6 gr. (0.4 gm.) of nembutal were used for analgesia in a single case, it was necessary to apply forceps in only twelve instances. Eleven of these were applied below the spines and one in the mid-plane; this was the largest baby in the group and weighed 7 pounds 12 ounces (3,522 gm.); the mother had a just minor pelvis with an anteroposterior diameter of 10 cm. and a biischial diameter of 8 cm.

It has been suggested recently that thyroid deficiency might play some part in the etiology of the toxemias of pregnancy. Patterson, Hunt, and Nicodemus<sup>12</sup> demonstrated both clinically and experimentally that the increased metabolism of pregnancy produces a subclinical hypothyroidism, which is accompanied by hypercholesteremia. When the maternal thyroid cannot produce sufficient thyroxin the fetal thyroid is drained; this constant depletion of fetal thyroxin produces a fetal hypothyroidism and hypercholesteremia. Fetal hypercholesteremia causes the deposition of cholesterol in the walls of the placental arteries, producing an endarteritis. If the endarteritis is severe, the arterial lumen will be occluded, resulting in placental infarction and

for this high incidence of negative cultures are: (1) that the bacteria contained within the abscess lose their virulence and die because of a deficiency of oxygen and poor nutrition, and (2) the active acquired immunity of the body kills the bacteria.

The source of the anaerobic organisms which were found in the pus of tubo-ovarian abscesses in our series would seem to be the lower genital tract, namely the vagina and cervix uteri.

Anaerobic streptococci have been repeatedly cultured from the vaginal tract by Krönig<sup>7</sup> (1895), Menge<sup>8</sup> (1895), Halle<sup>12</sup> (1898), Williams,<sup>9</sup> Schottmüller<sup>10</sup> (1911), Rosowsky<sup>11</sup> (1912), Schweitzer<sup>16</sup> (1919), Schmidt<sup>6</sup> (1919), Soule and Brown<sup>12</sup> (1932), and Carter and Jones<sup>13</sup> (1937) and others. Burt-White and Armstrong<sup>14</sup> cultured anaerobic streptococci from 35.9 per cent of 153 cervices.

Anaerobic streptococci had been isolated in 1897 and 1899 by Krönig and Menge from parametrial suppurations in infected puerperal cases. Schottmüller (1910) found the anaerobic *Streptococcus putridus* (later *putrificus*) in the pus of parametrial suppuration, purulent salpingitis, and pelvic abscesses, principally following septic abortions or puerperal cases. He raised the question whether the salpingitis in the observed cases was primarily caused by the *Streptococcus putrificus* or whether the latter was present as a secondary invader following primary gonococcal infection. He concluded that the anaerobic streptococcus could primarily cause salpingitis in spite of his invariable failure to produce experimental lesions with the strains he isolated.

Curtis<sup>15</sup> (1921) described anaerobic streptococci in five cases of adnexal or parametrial suppuration.

The high incidence of positive cultures in our series may be explained by: (1) the fact that anaerobic cultures were made on suitable media immediately after the pus was obtained at operation, and (2) the fact that these cultures were held under observation for a period of seven to twenty-eight days. Comparing Tables I and II a striking difference is noted between the number of negative aerobic cultures (70 per cent) and the number of negative anaerobic cultures (6 per cent). This emphasizes the importance of making prompt routine anaerobic as well as aerobic cultures.

Several hypotheses may be advanced to explain the presence of anaerobic organisms in these abscesses: (1) Bacteria present in the vaginal secretion may accompany the gonococcus in its ascent to the tube and may persist after the latter dies; (2) they may have the same mechanism of ascent as the gonococcus, and alone may be capable of setting up a state of prolonged inflammation and suppuration; (3) the abscesses may become secondarily infected from a neighboring adherent viscus such as the intestine. Satisfactory proof for any of these hypotheses is lacking.

It is difficult to explain a prolonged state of tubo-ovarian suppuration in the absence of viable microorganisms. Contributory evidence of the presence of such viable microorganisms may be found in three observations: The putrid odor of the pus in many instances, the occasional occurrence of deep wound abscesses after operation in the face of a negative aerobic culture of the tubo-ovarian abscess pus, and the development of a fatal peritonitis after salpingo-oophorectomy for

TABLE II. SHOWING INCIDENCE OF ANAEROBIC BACTERIA

ORGANISM	NO. OF CASES
1. Streptococci	22
2. <i>B. melanogenicum</i>	5
3. <i>B. pseudodiphtheriae</i>	4
4. Yeastlike forms	2
5. Unidentified gram-negative bacillus	1
6. Gram-positive streptobacillus	1
7. Negative cultures	2

could be grown under partial (CO<sub>2</sub>) tension or aerobic conditions. The latter therefore would seem to fit into that group of streptococci designated as "microaerophilic" by Meleney.<sup>1</sup> Two strains of these anaerobic streptococci were definitely hemolytic, one green producing, and all others nonhemolytic. They were all gram-positive after subcultivation, occurring in diploforms and short chains. Morphologically they seemed to fall into two subgroups, A and B; similar to groups A and B of Colebrook and Hare;<sup>2</sup> Group A being cocci of approximately the usual size of the common aerobic streptococcus, and Group B being micrococci extremely difficult to keep alive (see Table III). The organisms in Group A could be further classified by their ability or inability to produce putrid products during their growth. Those producing a putrid odor were apparently similar to the anaerobic *Streptococcus putridus* (later *putrificus*) described by Schottmüller<sup>3</sup> and later by Schwarz and Dieckmann,<sup>4</sup> and Schwarz and Brown.<sup>5</sup> Sugar fermentation studies did not permit further classification of these cocci. Taylor<sup>6</sup> stated that sugar fermentation tests were not likely to aid in their classification.

TABLE III. CLASSIFICATION OF ANAEROBIC STREPTOCOCCI ISOLATED IN THIS SERIES

## Group A:

gr +, short chained coccus with many diploforms of approximately the same size as the common aerobic streptococcus; obligate anaerobes; nonhemolytic.

I. Those capable of producing putrid products.

II. Those incapable of producing putrid products.

## Group B:

gr + micrococci occurring in short chains and clumps; very slow growing and difficult to keep alive; obligate anaerobes; non-hemolytic.

## Group C:

gr + hemolytic, obligate anaerobic coccus of approximately the same size as the common aerobic streptococcus.

## Group D:

gr + coccus, similar in size to those in Groups A and C; isolated by anaerobic methods and later grown aerobically or under partial (CO<sub>2</sub>) tension.

In ten instances an anaerobic streptococcus was the only organism recovered; in 7 cases it was associated with one other bacterium, in 2 cases it was found with 2 other bacteria, in 1 case with 3 other bacteria, and in 2 cases with 4 others.

The pathogenicity of these streptococci for laboratory animals was very low. Intraperitoneal injections in rabbits and guinea pigs did not produce fatal peritonitis. Small subcutaneous abscesses were produced in guinea pigs by 2 of the strains, while small areas of induration or no demonstrable lesions were produced by the remainder.

## DISCUSSION

The pus of chronic tubo-ovarian abscess has been reported to be bacteriologically sterile in the majority of cases as is shown in the collected series of cases in Table IV. The explanations that are given



There is some evidence that these bacteria, while usually existing as saprophytes in the mucous cavities of man, under favorable conditions may assume virulence. Notwithstanding the low virulence for laboratory animals, the frequent presence of anaerobic streptococci, often in pure culture in inflammatory states, such as puerperal sepsis, chronic Bartholin'sitis, appendicitis, peritonitis, pyelitis, pulmonary abscess, putrid empyema, endocarditis, and suppurative otitis media, strongly suggests their pathogenic nature for man.

#### SUMMARY AND CONCLUSIONS

1. The bacterial content of 25 consecutive cases of chronic tubo-ovarian abscess was studied.

2. The anaerobic streptococcus alone or associated with various other microorganisms was demonstrated in 22 of the 25 cases.

3. Negative cultures were found in only 2 of the 25 cases.

4. A series of cultures of tubo-ovarian abscess and pyosalpinx were collected from the literature.

5. The value of routine anaerobic as well as aerobic cultures is emphasized.

6. The importance of immediate cultivation and long incubation is stressed.

7. The pathogenicity of these anaerobic streptococci for man is suggestive, but has not been proved.

8. The presence of microorganisms growing in the pus of chronic tubo-ovarian abscess would seem to explain the characteristic recurrent attacks better than the assumption that the abscess becomes repeatedly reinfected from without.

The author wishes to express his indebtedness to Drs. J. P. Pratt and F. W. Hartmen for their supervision, aid, and criticism in the preparation of this paper.

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TABLE IV. COLLECTED SERIES OF CULTURES OF PYOSALPINX AND TUBO-OVARIAN ABSCESS\*

AUTHOR	NO. STERILE	GONOCOCCI	STAPHYLO- COCCI OR STREPTO- COCCI	TOTAL NO. OF CASES
1. Charrier	6	9		15
2. Hartman and Morox	13	13	4	33
3. Kelly	33	8	1	43
4. Legros	1			1
5. Martin	63	21	7	109
6. Menge	68	22	5	106
7. Orthmann	7	1		8
8. Prochnownik	5	1	21	27
9. Reichel		1		1
10. Schaffer	10			11
11. Schuta	69	23	15	109
12. Schmidt		1		1
13. Steman		1		1
14. Wertheim	72			116
15. Westermarck		1		1
16. Whiteside	9	7	3	27
17. Witte	15	7	4	39
18. Zweifel	32	8	3	44
19. Rist	3	2	1	7
20. Macheyrodt			1	1
21. Durk			1	1
22. Bellei	5	1	12	20
23. Walsh	9	7	5	25
24. Trommel			1	1
25. Andrews	26	5	2	42
26. Cosma	11			11
27. Joyle	35			39
28. Wiener			1	1
29. Noeggerath and Wertheim	122	56	17	312
30. Rosenow and Davis		1	2	3
31. Studdiford, Casper and Scodron	8	16		24
Totals	632 (53.6%)	212 (18.0%)	105 (8.9%)	1179

\*NOTE: Bacteria, other than gonococci, staphylococci, and streptococci, were not tabulated but were included in the total number of cases.

chronic tubo-ovarian abscess. In our series of 25 cases the pus had a foul odor in 10 instances. Cultivation of the anaerobes recovered produced a similar odor. The anaerobes which we believe were responsible for this foul odor were forms of the anaerobic streptococcus and the black-pigment-producing *B. melanogenicum*.<sup>16</sup>

The pathogenic power of anaerobic streptococci for man is difficult to determine. The great majority of investigators have found these bacteria to have little or no virulence for laboratory animals, with a few exceptions.

Wegelius<sup>17</sup> noted small intraperitoneal abscesses in mice after their injection. Marwedel and Wehrsig<sup>6</sup> produced an overwhelming infection in a guinea pig with a strain isolated from a war wound. Prevot<sup>6</sup> demonstrated pathogenic effects such as local abscesses, edema, or occasionally death with his strains. Harris and Brown<sup>18</sup> stated that three of their 57 puerperal fever strains killed mice in twenty-four hours. Colebrook and Hare<sup>2</sup> found that small subcutaneous abscesses were produced by 2 of their 7 strains recovered from puerperal sepsis.

TABLE I

	5-6 MONTHS UNITS	7-8 MONTHS UNITS	AT TERM UNITS		REMARKS
Average	6.45	11.74	16.82		Average of 100 pregnant women
T. J.	14.6	32.0	38.5	Twins	Suggested at 5½ months by high phosphatase. Proved by x-ray.
G. B.	11.0	15.7	22.0	Twins	Suggested at 6½ months by high phosphatase. Proved by x-ray.
M. D.	13.5	18.0	16.4	Twins	Twins suspected clinically as well as suggested by the high phosphatase.
E. H.	15.7	28.5	45.0	Twins	Suggested at 6 months by high phosphatase.
B. W.	-	22.8	29.5	Twins	Clinical and x-ray diagnosis at 8 months.
A. W.	-	22.0	25.8	Twins	Clinical and x-ray diagnosis at 8 months.
B. McD.	28.8	86.0	78.0	Single	Multiple pregnancy suggested by high phosphatase; x-ray negative; mother very anemic.
M. D.	-	13.0	-	Single	Miscarriage at 7 months. Petrified 4 months' fetus.
M. C.	-	8.5	-	Single	Clinical diagnosis possible twins; phosphatase suggested single pregnancy.
H. B.	4.5	-	-	Single	Family history of twins; phosphatase suggested single pregnancy. Miscarried at 7 months.
J. S.	4.0	-	-	Single	Clinical and family history suggested twins; phosphatase suggested single pregnancy.
S. H.	3.8	4.9	10.0	Single	Anencephalic infant stillborn. Low phosphatase led to the suggestion on the history of fetal anomaly.
B. T.	5.8	4.9	9.0	Single	Large spina bifida, Mongolian idiot.

## SUMMARY

Early findings in a study of the phosphatase of the blood in pregnant women suggest the possible value of this test in the diagnosis of twins.

Notes, B.: Routine Treatment of Gonorrhea in Females—Nonantiseptic Method, Med. Ann. Dist. Columbia 8: 111, 1939.

In August, 1933, treatment of gonorrhea in women was begun by creating a local reaction and drainage with the omission of antiseptics: (1) All cervixes with functioning cervical glands were cauterized one or more times with the electrocautery at intervals of two or more months in order to cause local reaction and to elicit better drainage of the active focus. (2) The urethral meatus and cervix were treated weekly with applicators saturated with 25 per cent silver nitrate in order to cause local reaction and to favor better drainage. (3) Douches of 1.5 per cent acetic acid (vinegar or physiologic) were taken by the patient at home twice daily with a fountain syringe until the cervix was healed and with a pressure syringe (bulb type) after the cervix was healed. Of 3,394 women with gonorrhea admitted as new cases to the gynecologic section of the Social Hygiene Clinic of the District of Columbia 705 were discharged as cured by the foregoing method. The author concludes that antiseptics should be abandoned in the treatment of gonorrhea in women and that every patient who cooperates can be cured.

J. P. GREENHILL.

# BLOOD PHOSPHATASE IN PREGNANCY AN INDICATION OF TWINS

## A PRELIMINARY REPORT

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DURING the course of a nutritional study of pregnant women attending the Prenatal Clinic of the Toronto General Hospital, estimations of the plasma phosphatase\* have been made by the method of King and Armstrong,† with modifications for the Evelyn colorimeter. The results of these determinations have shown that between five months and six months in pregnancy the phosphatase averages 6.4 units in 100 patients, few readings being below 4 units or above 9 units.

The possibility of a twin pregnancy was suggested when a reading of 14.6 was obtained in a patient three months before term. At this time, physical examination had not suggested twins. However, subsequent x-ray proved their presence.

Table I gives the findings in six twin pregnancies and those single pregnancies with abnormal or interesting phosphatase values.

✓Twins were suggested or confirmed in six cases by phosphatase readings more than double the average during pregnancy. Single pregnancies were suggested in three cases by normal phosphatase readings, where clinical examination and family history suggested twins. In one patient (B. McD.), unusually high phosphatase values were found throughout the last four months of the pregnancy. X-ray and finally delivery at term revealed the presence of a single normal fetus. The only abnormality found was moderate anemia throughout pregnancy. Other estimations upon the blood were as follows: Nonprotein nitrogen, 30 mg. per cent; calcium, 9.9; phosphorus, 5.0 mg. per cent. In this case there was no clinical evidence of biliary obstruction or liver disease.

\*Phosphatase is an enzyme which is found where calcareous deposit normally takes place. It hydrolyses phosphoric acid ester and sets free inorganic phosphate. Growing bone has a high phosphatase activity, while cartilage has none. The formation of bone depends upon the concentration of calcium and phosphate, and also upon the hydrogen ion concentration of the tissue fluids. This enzyme is also found in the kidneys, blood, intestinal wall and liver.

The normal adult range (King and Armstrong) is between 3.7 and 13.1 units, the majority being between 5 and 10 units. Serum phosphatase has been found elevated in diseases characterized by marked osseous changes, such as osteoporosis, osteomalacia, Paget's disease, marked parathyroid hyperfunction, and local bone atrophy. It is also elevated in diseases of the liver, such as biliary obstruction, hepatitis, and cirrhosis of the liver.

†King, E. J., and Armstrong, A. R.: *Canad. M. A. J.* 31: 376, 1934.

Three days following this severe reaction, the patient's hemoglobin was down to 38.4 per cent, R.B.C. 1,840,000. Condition was naturally alarming, in view of the fact that the kidneys were not functioning, and the hemoglobin was very low. Another donor was selected, and another citrate transfusion attempted, and carried out successfully, patient receiving 500 c.c. of citrated blood without undue reaction.

All known means to stimulate kidney function were attempted, including calcium chloride intravenously, diathermy over kidney regions, and 50 per cent sucrose solution intravenously in quantities of 50 to 100 c.c.

Dr. Frank Hinman was called in consultation on the fifth postoperative day, and he suggested giving Fisher's solution, 1,000 c.c., intravenously twice a day. The bladder was irrigated with a 4 per cent boric solution, and following the first twenty-four hours of Fisher's solution, intake by mouth was 2,520 c.c. and output by catheter was 90 c.c. Small doses of Epsom salt were given by mouth and about the seventh day patient was quite edematous. However, fluid intake was kept up to 1,500 c.c. for twenty-four hours. Patient was not able to take very much by mouth because of nausea. Output gradually increased to 120 c.c. for twenty-four hours, and 255 c.c. and then finally on the tenth day output had increased up to 645 c.c., and the patient's condition gradually improved, despite the fact back and legs were still very edematous, and she complained of weakness and great difficulty in breathing, with considerable pain in lower lumbar region still present. On the eleventh postoperative day patient voided over 5,000 c.c. of urine.

Patient was definitely on the mend until the fourteenth day, and for no reason whatsoever, the patient's pulse went to 166, she became very dyspneic, and the medical consultant made a diagnosis of paroxysmal nodal tachycardia, with suggestive evidence of myocardial damage. Quinidine was administered for this condition, also coramine in fairly large doses until pulse gradually came down to 128 and remained between 128 and 140 for the next ten days.

Patient was eventually discharged on the twenty-sixth day in a weakened condition, but considerably improved.

#### COMMENT

Although the blood donor and recipient were cross-typed and said to be entirely compatible, this patient developed a blood-transfusion reaction, confirming the idea that the agglutinin content of some donors' blood sera may be so surprisingly high, namely, 1:200 instead of the usual 1:3; that serious results may ensue unless high titer sera are used when cross-typing the blood before transfusion. Cross-matching between patient and donor was rechecked on two different occasions following this reaction and the blood was found compatible.

We do not know whether this patient's kidneys responded to the Fisher's solution, which was given intravenously over a period of three to four days, or whether it was a combination of the Fisher's solution plus other things used to stimulate kidney function. The fact remains the patient got well.

Blood chemistry was not done due to the economic factor involved.

It is now about six months since the patient left the hospital, and on examination on different occasions, we find her in good physical condition. Her last urinalysis was perfectly normal and her blood count showed an 84 per cent hemoglobin with 4,110,000 red blood cells.

A kidney function test was done, dye being injected intravenously with the following results:

First specimen 30 minutes after injection	40 per cent
Second specimen 60 minutes after injection	20 per cent
Third specimen 90 minutes after injection	10 per cent
Fourth specimen 120 minutes after injection	5 per cent
Total	<u>75</u> per cent

Blood chemistry at this time showed a nonprotein nitrogen of 35 mg./100 c.c. blood.

## ANURIA FOLLOWING BLOOD TRANSFUSION

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FOREIGN literature repeatedly describes certain reactions which occur after nearly every major transfusion. Besides albuminuria and hemoglobinuria,<sup>2</sup> a grave or even fatal renal complication may follow in the form of diminution up to complete suppression of the urinary flow.<sup>1, 3-5</sup>

These grave transfusion dangers are charged to the reaction between the donor's erythrocytes and the recipient's plasma. The mechanical effect of these group reactions, agglutination and hemolysis, is connected with a more or less complete embolic blockade of the capillary circulation, especially in the kidney.<sup>6, 7</sup>

The mutual reaction of different blood types manifests itself in the first place as agglutination, and second may be followed by a hemolytic phase. According to this interpretation, the two phenomena are closely interrelated; they appear as the components of an identical reaction, and the hemolysis is always preceded by agglutination. The "disagreement" of two blood types is the expression of a reaction between the agglutino-gen-agglutinin complex of the mixture (Dyke).<sup>6, 7</sup>

I would like to report a personal case wherein anuria followed a citrate transfusion, only 60 c.c. of blood being administered.

A multipara, aged 30 years, was brought into the hospital in shock following incomplete, accidental miscarriage, large amount of blood being lost. Under anesthesia uterine cavity was packed. Nothing further was done and patient returned to bed. Blood count on entry showed 63.8 per cent hemoglobin with 3,590,000 red blood count. White count 23,750 with 93 per cent neutrophils and 7 per cent lymphocytes.

Within twenty-four hours the patient's hemoglobin was 44.6 per cent, red cells 2,580,000. In view of this it was decided to give the patient a citrate transfusion. A donor was selected, and by laboratory tests the patient's serum and donor's cells showed no agglutination, and patient's cells and donor's serum showed no agglutination. Blood Wassermann was negative.

Transfusion was started, and after administering only about 60 c.c. of blood, the patient complained of severe pain in her back, difficulty in breathing; pulse rate was 160 and patient appeared in extremis. Transfusion was immediately stopped and adrenalin was administered. Patient vomited considerable yellow fluid. She was treated for shock, and it was about one and one-half hours before she responded. She was not bleeding through pack, so vaginal packing was removed, following which large pieces of placental tissue were passed spontaneously.

Patient was given glucose intravenously 1,000 c.c. of a 10 per cent solution. Prior to her transfusion, patient had voided spontaneously, passing various quantities of urine, in fairly good sized amounts. The urine analysis on entry was essentially normal. Following the transfusion, and the severe reaction which the patient experienced, the urinalysis showed a two-plus albumin, hyaline and fine granular casts and a specific gravity of 1.007. There were no red blood cells present, but the field was loaded with white blood cells. Patient was catheterized and 980 c.c. of urine were obtained. Twenty-two hours after transfusion patient passed only 120 c.c. of urine despite fluid intake of 1,500 c.c.

It was noted that there was a gradual diminution of urine for the next forty-eight hours, varying from 250 c.c. to complete suppression. However, the patient's temperature and pulse appeared normal. She had no complaints with the exception that she could not urinate, and despite the administering of hypertonic glucose intravenously in small quantities, and giving salt solution by hypodermoclysis, only 30 to 40 c.c. of urine could be obtained by catheter in twenty-four-hour output.

## GROUP II. ARTIFICIAL MENOPAUSE

This group of 29 patients complained of postoperative or postradiation menopausal syndrome. Various combinations of the symptoms enumerated in the previous group were manifested by these patients, but were usually more severe in character. The basic therapeutic regime of 1 mg. three times a day orally was instituted, and individualized subsequently when necessary. Of the 29 patients included in this group, varying in age from 25 to 54 years, 27 were improved, 1 was unimproved, and one failed to continue therapy.

## GROUP III. HYPOESTRINISM

There were 8 patients ranging from 24 to 34 years of age, manifesting symptoms attributable to estrogenic insufficiency. Their symptoms included nervousness, dizziness, hot flushes, irritability, frigidity, headache, insomnia, and muscle and joint pains. In addition, there were one case each of dysmenorrhea, dyspareunia, and menstrual edema, and 2 patients reporting severe premenstrual breast pain. The administration of the drug was varied in accordance with the time of appearance and the severity of the symptoms. All of this group showed marked improvement.

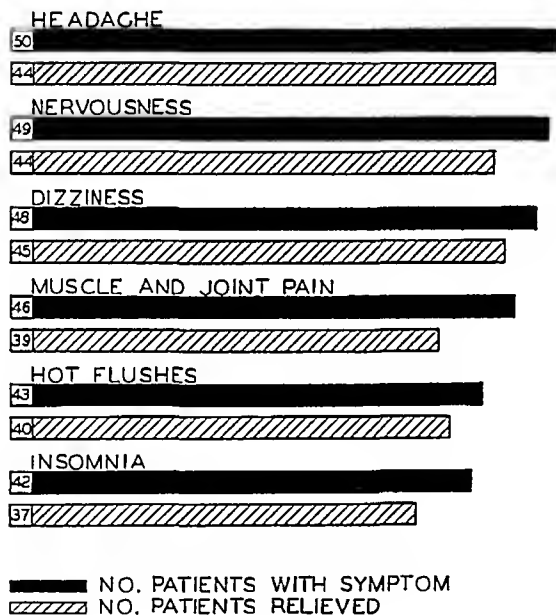


Fig. 1.

## DISCUSSION

The frequency of nausea noted in our early experiences with oral administration of stilbestrol prompted us to seek to relieve this distressing symptom which often was the cause of rebellion on the part of the patient. At first we used soda bicarbonate, 4 Gm. given concomitantly and later, soda mint tablets. However, the results were not universally satisfactory. Upon the suggestion of a colleague,<sup>2</sup> working with oral administration of stilbestrol in children, we prescribed the tablets, powdered and mixed in a glass of milk. Nausea has been satisfactorily controlled in this manner, in the majority of the cases. No other untoward effects have been recorded in any case. In a few cases fullness of the breasts was present, but not to a distressing degree.

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## THE ORAL ADMINISTRATION OF STILBESTROL

## (SECOND CONTRIBUTION)

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IN A previous communication<sup>1</sup> we presented our results, using a new synthetic estrogen, stilbestrol, in the treatment of syndromes presenting signs of estrogenic deficiency. Since the results obtained were as satisfactory with stilbestrol as were previously experienced with biologic estrogens administered hypodermically, we were prompted to continue our studies.

Our clinical experience with orally administered biologic estrogens has been unsatisfactory. However, the desirability of utilizing this mode of administration and our previous success with stilbestrol by the intramuscular route, led us to investigate the value of this drug given orally.

Our clinical material consists of 57 cases from the Hutchinson Memorial Clinic of Tulane University of Louisiana and the private practice of three of us (J. C. W., B. B. W., C. G. C.). In this group of 57 cases, there were 20 classed as having a physiologic menopausal syndrome (Group I), 29 had postoperative or postradiation menopausal syndromes (Group II), while 8 cases were classified as manifesting hypoestrinism (Group III).

## GROUP I. PHYSIOLOGIC MENOPAUSAL SYNDROME

The physiologic menopausal syndrome group consisted of 20 patients ranging in age from 35 to 51 years. Their complaints included various combinations of the following symptoms: headache, dizziness, nervousness, hot flushes, depression, muscle and joint pain, frigidity, insomnia, irritability, and vaginitis.

Routinely our patients were given 1 mg. of stilbestrol three times a day, orally. This dosage was adequate for the control of symptoms in the majority of cases, and as improvement was noted, the dosage and frequency of administration were diminished. A few patients were adequately controlled with as little as 0.1 mg. per day. If improvement was not satisfactory, the dosage was increased to as much as 15 mg. a day.

Of the 20 patients in this group, 17 were clinically improved, 2 reported slight improvement, and 1 was unimproved.



degeneration. Toxins absorbed from this degenerating placental tissue produce clinical eclampsia with convulsions in the mother. In this group it is of passing interest that there were no cases of eclampsia or pre-eclampsia.

#### SUMMARY

One hundred and sixteen women were given daily doses of from 3 to 6 gr. (0.2 to 0.4 gm.) of desiccated thyroid extract during four or more months of their pregnancies without qualitative or quantitative food restrictions. One hundred and sixteen normal babies having an average birth weight of 6.8 pounds (3,090 gm.) were delivered. The mothers demonstrated no signs of hyperthyroidism, pre-eclampsia, or eclampsia, and they gained an average of 18.2 pounds (8.3 kilograms) during their pregnancies.

#### CONCLUSIONS

This series is too small to reach any final decision regarding the merits of this treatment; however, the results to date are encouraging and merit further study by those who might be interested.

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## TREATMENT OF METROMENORRHAGIA WITH TESTOSTERONE PROPIONATE

### A PRELIMINARY REPORT

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THE purpose of this report is to present our experiences with the use of testosterone propionate in the treatment of metromenorrhagia. Here we are particularly concerned with the average minimal dosage necessary to control the excessive bleeding.

The therapeutic rationale for the use of testosterone propionate will be fully reviewed elsewhere.<sup>1</sup> Briefly summarized, the following considerations appear pertinent. The effects of testosterone on the endometrium are variable. A progestational response may be elicited, for example, in the rabbit,<sup>2</sup> but apparently not in the monkey<sup>3</sup> or human being.<sup>4</sup> Hypoplasia of the endometrium may result from chronic in-

The results of oral administration of stilbestrol in the alleviation of individual symptoms is summarized in Fig. 1. Improvement is usually noted within a week. Many of the patients included in this series had been treated previously by stilbestrol hypodermically, and were then maintained satisfactorily by the oral route. Comparatively few patients had previous biologic estrogenic preparations, and the change to stilbestrol was more than satisfactory. Discontinuance of therapy occasions recurrence of symptoms within two weeks, necessitating re-institution of therapy. Withdrawal bleeding was noted in two patients who had long been amenorrhoeic.

No influence upon normal menstrual cycles was noted in this series.

Our observations in the oral administration of stilbestrol in cases of menopausal syndromes, physiologic and artificial, and hypoestrinism, lead us to recommend:

1. That therapy be individualized.
2. That the initial dosage be at least 1 mg. three times a day, and be varied as indicated.
3. When symptoms are improved that the amount be reduced to a satisfactory maintenance dose.
4. That the tablets be powdered and administered in milk.

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### SPONTANEOUS OCCLUSIVE PYOMETRA

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PYOMETRA is of fairly uncommon occurrence and it is usually associated with cervical stenotic conditions, such as strictures resulting from childbirth, cervical operations, radiation, gonorrheal infection, and malignant infiltrations.

In women past the menopause, senile vaginitis is commonly encountered.<sup>1</sup> Shortly after the last menstrual period there begins a gradual atrophic development with the accompanying closure of the cervical canal and diminution of the size of the vaginal vault. These changes are the result of the failure of ovarian secretions which produce a terminal cicatricial closure of the cervical canal. With the occlusion of the canal, there is first a gradual retention of mucoid secretion followed by a contamination of this material. Nothing is noticed or complained of except possibly a sense of suprapubic fullness and pressure. When this pressure has become sufficient to overcome the pre-existing occlusion of the cervical canal, a gradual seepage of purulent material is noticed by the patient. Sometimes the escape of this retention is of sufficient quantity to afford spontaneous and complete relief for a short period of time. Operative interference alone seems to produce a cure.

Further mention should be made of the fact that females in the childbearing age have cervical strictures. A negative history of infection or instrumentation is obtained. Birth trauma can be ascribed as the cause with the usual sequence of retention followed by infection and either the appearance of a palpable suprapubic

mass or complaints of low abdominal pressure, pain, and cramps. A case of pyometra complicating pregnancy was reported by Gemmill.<sup>2</sup> In another instance an infected pregnancy in a 28-year-old female was suspected by Pride.<sup>3</sup> At operation the cause was found to be a necrotic fibroid. A case of pyometra complicated by dermoid cyst twisted on its pedicle was reported by Godlewski.<sup>4</sup>

Malignant infiltrations of the cervical canal occur as in an endophytic type of cancer. The lumen is occluded with the resulting retention. There is a gradual foul discharge which leads to an investigation of its cause. Dilatation of the cervix is often found to be difficult, but immediate results and relief are obtained when the cervical canal is patent. Cancerous cells are found in the pathologic study. Reeb<sup>5</sup> gives an account of a single case of pyometra, the genesis being a calcareous concretion in the neck of the uterus and obstructing it. Loranger<sup>6</sup> calls attention to a case of noninfectious pyometritis produced by injections of large amounts of highly potent estrogenic substances.

#### CASE REPORT

M. G. S. (Unit No. 2135), aged 73 years, was admitted the first time to this hospital on Nov. 2, 1937 with a complaint of foul, bloody leucorrhea over a period of several weeks. The present illness was vague but was consistent in that the vaginal discharge was gradual in onset. Past and family histories were irrelevant.

*Physical Examination.*—Temperature 99.4° F., pulse 108, respirations 20, blood pressure 155/80. She was an elderly, poorly nourished woman. There was a partial denture and a marked pyorrhea. Neck revealed no adenopathy or abnormal pulsations. Examination of lungs revealed bronchovesicular breath sounds, no râles, or friction rubs. Percussion note was normal. Heart sounds were of fair quality. There were no murmurs. Breasts were flabby. Abdomen was below the thoracic plane and somewhat tender in the suprapubic and both adnexal regions. Normal peristaltic sounds were elicited on auscultation. Vaginal examination revealed an atrophic vaginitis, marital introitus, a very short, atrophic cervix, and a uterus that was twice normal size and tender on palpation. No palpable masses were present in either adnexal region. There was a moderate amount of foul, purulent discharge. The remainder of the physical examination was not remarkable.

#### *Diagnosis.*—Pyometra.

Laboratory examinations: Red blood count, 4,000,000; hemoglobin, 79 per cent; white blood count, 8,700; polymorphonuclears, 71 per cent; lymphocytes, 27 per cent; monocytes, 2 per cent. Wassermann and Kahn tests were negative. The urine was clear; specific gravity, 1.005; acid in reaction; sugar and albumin, negative; the sediment showed an occasional hyaline cast.

Two days after admission the patient was examined. The cervix was found to be atrophied, but the os was large and externally patent. A uterine sound was gently inserted and no apparent strictures were encountered. Approximately 3 to 4 ounces of purulent material exuded from the cervix. This was cultured and smeared. The culture showed mixed organisms, but the smear was positive for gram-negative intracellular diplococci. Following operation, the temperature rose to 100.4° F. for two days and then fell to normal. The patient gradually ceased passing any purulent material per vaginam and was discharged improved on the tenth hospital day. No other operative interference was believed justifiable because of her age. She was advised to return to the gynecologic out-patient clinic for follow-up. This she did twice and on both visits she still had a slight but persistent foul, purulent discharge. Her abdomen was negative on palpation. She then stopped coming to the out-patient clinic of her own accord.

On Nov. 8, 1939, patient again appeared in the out-patient clinic with the complaint of being unable to void except for a little dribbling. She was catheterized, but only 30 c.c. of urine was obtained. On vaginal examination a cystic mass 8 by 10 cm. was palpable. Admission to the hospital was advised with the provisional impression of pyometra.

She was admitted to this hospital with the complaint of not being able to void, a sensation of dull pressure in the pelvis, and a foul, purulent vaginal

discharge. These complaints dated back some three to four months previous to admission. Patient stated that during the night previous to admission she had saturated her nightgown and bedclothes by a profuse purulent discharge and estimated the amount to be a pint. Purulent discharge without blood had continued up to the present.

*Physical Examination.*—Temperature was 98.2° F.; pulse, 88; respiration, 24; blood pressure, 138/80. Patient was in no apparent distress. The examination was similar to the one two years previously except for definite tenderness in the suprapubic region and in both adnexa. There was a foul, purulent discharge per vaginam. Examination revealed a short, firm cervix; os was palpable just behind the cervix in the cul-de-sac. Exquisite tenderness was elicited on attempting to bring the fundus of uterus out of the cul-de-sac, and the attempt was unsuccessful.

*Laboratory Examinations.*—White blood count was 10,400; polymorphonuclears, 61 per cent; lymphocytes, 37 per cent; eosinophiles, 2 per cent. The urine was slightly cloudy, amber, acid in reaction, negative for sugar, but with a decided trace of albumin present. Smear of the discharge showed many pus cells, mixed bacteria, and a moderate number of extra- and intracellular gram-negative diplococci. The sedimentation rate was 23 mm. in one hour. Electrocardiogram revealed a sinus rhythm, ventricular rate 120, normal conducting mechanism.

The staff again was of the opinion that this patient had a pyometra. The patient was removed to the operating room and under nitrous oxide gas anesthesia a uterine sound was passed into the cervical os. The sound was introduced approximately three-quarters of an inch, at which time there escaped 6 ounces of pus. No obstruction was encountered. A smear and culture were taken. The uterine cavity was curetted with a dull curette. Patient was returned to the ward in good condition.

*Pathologic Report.*—(No. 17777.) Gross: Several bits of yellow slightly firm tissue. *Microscopic:* Small pieces of endometrium showing very few glands, all of which were benign. There was a heavy leucocytosis, some edema, and hemorrhage. Also a number of the stroma cells were swollen and had a pale-staining, foamy cytoplasm. *Diagnosis after gross and microscopic examination:* Infectious endometritis.

Smear reports showed many leucocytes, mixed bacteria, and a few extra- and intracellular gram-negative diplococci. Cultures revealed many mixed bacteria.

The patient was given a high caloric diet, vitamin and sulfanilamide therapy. A few days after admission the blood sulfanilamide level had reached 9 mg. per cent. The sedimentation rate changed to 31 mm. in one hour. No gram-negative diplococci were found in cervical smears at this time. Sulfanilamide was discontinued, and on the nineteenth hospital day the patient was discharged improved. At this time she was strongly advised to return to the out-patient clinic at regular intervals for follow-up observation and treatment.

Since discharge she has been to the clinic regularly. Cervical smears reveal an occasional gram-negative extra- and intracellular diplococcus. When last seen three months after her discharge from the hospital, the uterus was found to be in anterior position, mobile, of average size and unaccompanied by pain or tenderness. The cervical canal was patent without any further evidence of drainage and the smears were negative for the presence of gram-negative extra- and intracellular diplococci.

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## PREGNANCY COMPLICATED BY FIBROMYOMAS OF THE LOWER UTERINE SEGMENT

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**W**HILE fibrotic conditions of the uterus are not uncommon in pregnant women, it is relatively rare to find large fibromyomas in the lower uterine segment of a pregnant uterus at or near term. The following is such a complicated case.

Mrs. G. H., para ii, gravida iv, was admitted to the hospital April 16, 1939.

*Past History:* In 1929 the first child was delivered spontaneously after labor was induced three weeks prematurely by the insertion of a bougie because of hypertension and marked edema. There were no headaches nor visual disturbances. The post-partum course was uneventful. In 1932 a dilatation and curettage was done to interrupt a one and one-half months' pregnancy because of pernicious vomiting which resulted in marked dehydration. In 1932 she had a spontaneous abortion at three months. In her childhood the patient had measles, chicken pox and scarlatina.

*Family History:* Her mother and father both died of cancer. A sister had a hysterectomy for uterine fibromyomas. Her menstrual periods began at 14 years of age, regular twenty-eight-day cycle, with four- to five-day duration of the periods. Last menstrual period, Aug. 17, 1938. Term date estimated as May 23, 1939. She gained 26 $\frac{1}{4}$  pounds in weight (128 pounds to 154 $\frac{1}{4}$  pounds). Her appetite was good and bowels were regular. She had marked nausea and vomiting during the first three months, requiring hypodermic medications for sedation. There was moderate leucorrhea but no history of bleeding or dysuria during pregnancy. She had experienced urinary frequency and nocturia prior to admission. For one month before admission, there was edema of the feet and ankles. For three days before admission the patient had severe headaches and slight nausea. There were no visual disturbances.

*Physical Examination:* The blood pressure was 178/106. The patient was a white, well-nourished female. Uterus was the size of an eight months' pregnancy. Fetal heart tones were 148, left upper quadrant. There was slight edema of feet and ankles. Otherwise the physical examination was negative. The heart was normal.

On April 16, 1939, the patient was admitted at 10:30 A.M., with a blood pressure of 192/112, pulse 92. One and one-half grains of nembutal were given. During this day the blood pressure ranged between 162/110 and 178/108.

*Urinalysis:* Specific gravity 1.015, reaction neutral, albumin heavy cloud, sugar 0, acetone 0, casts very rare hyaline and granular, leucocytes moderate amount, many epithelia. Hemoglobin was 80 per cent and red blood count 4,130,000.

On April 17, 1939, the blood pressure ranged between 174/110 and 144/96, and the urine showed heavy cloud of albumin every day with a few casts.

On April 21, 1939, the patient was examined vaginally, but it was impossible to identify the cervix or its external os. She was taken to the delivery room for a more complete examination, but still the cervix could not be found.

After April 23, 1939, the blood pressure ranged between 144/92 and 192/104. The urine continued a consistently heavy cloud of albumin with a few granular casts. She was having a salt-free diet and 1 ounce of magnesium sulphate every morning. The trend of the blood pressure and the results of the daily urinalysis did not indicate any improvement in the patient's condition.

On April 29, 1939 at 7:30 P.M. the patient began to have a slight bloody show and few cramplike pains.

On April 30, 1939, at 10:00 A.M. the patient was having pains every fifteen minutes with good contractions. The fetal head was floating above the inlet, and the fetal heart sounds were 148 on the left side of the abdomen above the navel. At 10:00 P.M. the blood pressure was 174/124. The baby's head was still high and the intern noted that there seemed to be some obstruction to the progress of the fetal head into the inlet. The uterus was oddly shaped. Some mechanical obstruction to the normal progress of labor seemed apparent, such as a cervical fibroid.

On May 1, 1939, at 12:02 A.M. the patient was taken to surgery and delivered of a living 5-pound 4-ounce female child by classical cesarean section. The uterus was closed after delivery of the child, and a panhysterectomy was performed. There was a large fibroid present on the posterior wall of the cervix which was 12 cm. in diameter. Another large fibroid was also present.

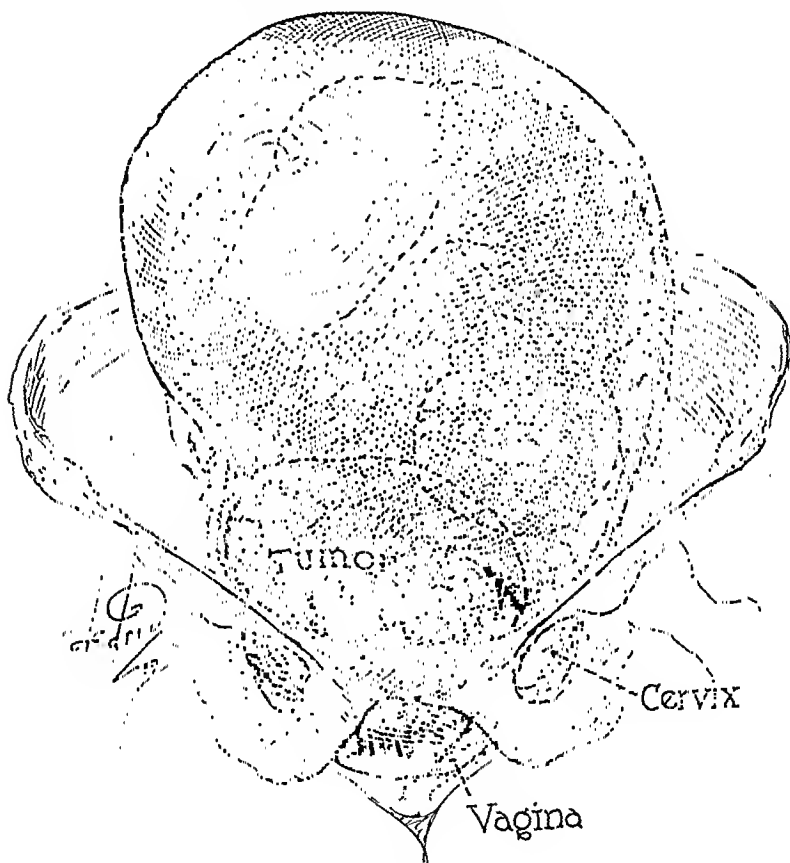


Fig. 1.

The blood pressure on return from the operating room was 164/130. The highest temperature postoperatively was 100° F. on the third day. The pulse during the day of the operation and through the fifth postoperative day ranged between 84 and 120.

On May 4, 1939, the third postoperative day, about 1:00 P.M., the patient became apprehensive and developed blurred vision. The blood pressure was elevated to 216/136 and the pulse was 120. One-fourth grain of morphine sulphate was given, followed by  $\frac{1}{2}$  c.c. doses of *Tr. veratrum viride* at 3:15 P.M. At 4:45 P.M. the blood pressure was down to 94/62, and it reached its lowest level of 80/58 at 5:45 P.M. The pulse was 68. At 8:00 P.M. the patient complained of pain in the right hypochondrium. At 9:00 P.M. the blood pressure was 146/96, pulse, 92. On May 5, 1939, at 8:30 P.M., the patient again complained of pain in the right hypochondrium. This later moved to the right lumbar area. The patient was voiding

satisfactorily. Urinalysis showed heavy cloud of albumin, no casts, and otherwise negative.

On May 16, 1939, at about 5:00 P.M., the patient began to experience a very chilly feeling and the pulse became extremely rapid (160 at 7:00 P.M.). The temperature rose to 104.2° F. Thereafter the temperature gradually returned to normal. Systolic blood pressure remained around 130 and the urine still showed evidence of nephritis.

The patient was discharged on the twenty-fifth day. Her family doctor reports that with the exception of an occasional cloud of albumin in her urine, she is in good condition.

#### COMMENTS

Demonstrable tumors of the upper uterine segment are relatively more frequent during pregnancy than is generally supposed, but, as a rule, do not cause serious trouble during delivery.

Tumors of the lower uterine segment appear to be infrequent, but when present, during pregnancy at term, challenge the ingenuity and skill of the obstetrician. While it is well known that tumors of the lower uterine segment may be pulled up out of the pelvis into the abdomen by the upward traction of the fundus, this case demonstrates that occasionally this does not happen and obstruction to delivery is the result.

This patient seemed to have had none of the usual prenatal symptoms of fibroma complicating pregnancy, such as discomfort, pain, bleeding, and pressure symptoms, but was brought into the hospital and treated by her family physician, Dr. Wm. Jones, for a toxemia of pregnancy, which evidently from her history, was a toxemia of the nephritic type.

During the medical treatment of the toxemia, fibroids were not suspected, and it was not until the onset of labor that the intern and the family physician noticed the abnormal shape of the uterus during contractions, and consultation was sought. A definite hard mass had appeared above the symphysis which had pushed the head higher up and anterior. The fetal heart sounds remained rapid in the upper left quadrant.

At this time the cervix could not be located by vaginal examination but a hard mass could be felt higher up. Realizing that an obvious mechanical dystocia was present after the possibility of a twin pregnancy, an ovarian cyst or an overdistended bladder was ruled out, it was evident that we were dealing with a large fibroma or fibromas of the lower uterine segment and that during labor the lower uterine segment was partially pulled up and the uterus had rotated. This torsion or partial rotation of the uterus pulled the fibroids, which were posterior and lateral, into more of an anterior position, so that they could be felt above the symphysis.

A high classical cesarean section was immediately performed, after which it was discovered that the tumor mass could be dislodged and removed. This was done. Fig. 1 illustrates the size and extent of the fibroids and the impracticability of leaving the uterus.

The patient recovered after a stormy convalescence and returned home with a live baby.

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## CARCINOMA OF THE CERVIX IN A SEVEN MONTHS OLD INFANT\*

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CARCINOMA of the cervix is considered a malignant disease of adult life, generally occurring in a previously traumatized cervix. Therefore, its appearance at the age of seven months is startling and unusual, and difficult to interpret in terms of precipitating factors and carcinogenesis.

Cervical carcinoma in the early years of life is extremely rare. There is but one recorded case occurring in the first year of life, Bertkau's epidermoid carcinoma of the cervix and vagina in a seven-month-old child, confirmed by Robert Meyer. Meyer also confirmed Glockner's case of adenocarcinoma of the cervix in a seven-year-old child. Ganghofer's case of uterine carcinoma occurred at eight years and Bouner's at thirteen years.

The case herein reported is that of a baby in whom the symptoms of cervical cancer appeared at the age of seven months, was diagnosed positively by biopsy at nine months, and was followed through laparotomy, external and internal radiation, to autopsy fifteen months after the first symptom of cancer appeared.

Baby S. was born Feb. 21, 1937, normal spontaneous delivery at term, labor of twenty-seven hours, of a primiparous, 21-year-old, white female. Ante-partum course was normal; family history was negative for malignant disease. At birth the child showed no evidence of abnormality and weighed 3,190 Gm. (7 pounds). The neonatal period was normal. She was breast fed for eight months and then weaned.

On September 25, when seven months old, fresh blood was noted on a dry diaper, and on Oct. 1, 1937, blood was noted coming from the genitalia. This occurred again in November and on Dec. 1, 1937. When seen in December it was thought advisable to inspect the vagina, since the late onset of bleeding in infant life and the prolonged period of spotting seemed to rule out the physiologic bloody discharge occasionally seen neonatally. Through a Cameron nasal and aural speculum a polypoid growth about the size of a pea, purplish red and bleeding easily, was seen on the cervix.

A biopsy was taken and the pathologic report returned was adenocarcinoma of the cervix. This was noted to be highly undifferentiated.

The baby was admitted to hospital Jan. 10, 1938, for further examination, and was symptomless except for a brownish vaginal discharge. The weight was 9,450 Gm. (20 pounds 14 ounces). On January 15 another cervical biopsy was obtained and the same report was returned. This biopsy showed a great variety of nucleated cells, very numerous mitotic figures, and numerous blood vessels. Diagnosis: Carcinoma of the cervix.

The potential effects of radiation upon the child's development were considered. An operative attempt to conserve ovarian function was planned and performed Jan. 15, 1938. A low midline approach to the abdomen showed that the adnexa and uterus were normal. A small mass was palpated in the vagina in the region of the cervix with no signs of intra-abdominal metastases, indicating that the growth arose in the vaginal portion of the cervix. The left utero-ovarian ligament was divided, and the ovary carefully dissected with the mesovarium, avoiding the ovarian plexus at the hilum. This permitted the left ovary, attached only by the infundibulo-pelvic ligament with its blood supply, to be carried laterally two-thirds of the way from the pubes to the umbilicus, and there attached to the peritoneal aspect of the anterolateral abdominal wall. The postoperative course was uneventful.

\*Presented at a meeting of the New York Obstetrical Society, January 9, 1940.



Radium therapy was begun six days postoperative, Jan. 21, 1938. The cervix was crossfired from five directions in 3,000 mc. doses; on January 21, to right and left groins; on January 22, to right and left trochanteric regions; and on January 23, to the lower sacral region, a total of 15,000 mc. hr. The transplanted ovary was carefully protected with adequate lead screens during the series of anterior treatments. There were two slight elevations of temperature during this period, to 101.6° and 100.4 F., for one day each, but no other systemic reactions. All vaginal discharge stopped one week from the date of the last treatment.

One week after the last treatment the vagina was inspected, using a Cameron nasal speculum. The cervix appeared normal, but there was a granulomatous-appearing area in the left fornix. Two weeks later biopsies were taken under direct vision, from the cervix and the left fornix. These both showed the changes of necrosis and chronic inflammation, but no evidence of malignancy.

During this stay in the hospital, from January 10 to February 27, the child appeared generally well. The discharge weight was 9,250 Gm. (20 pounds 6 ounces). The blood count on admission showed 87 per cent hemoglobin, 4.0 million red blood count; 18,000 white blood count with 65 per cent lymphocytes and 30 per cent neutrophils; one week following radiation it showed 80 per cent hemoglobin, 3.9 million red blood count, and 4,100 white blood count with 72 per cent polymorphonuclears and 22 per cent lymphocytes.

On March 14, 1938, the child returned, weighing 9,400 Gm. (20 pounds 12 ounces), which weight she maintained during the stay. April 1, 1938, the cervix was inspected and slight edema with telangiectases of the anterior lip was noted, together with cicatrization of the left fornix. At that time a small radium bomb was placed in the vagina, and a dose of 240 mc. hr. was given directly to the cervix. No immediate reaction was noted and the child was discharged on the next day.

During weekly observations in April and May she received four intramuscular injections of reticulogen in an effort to build up her red blood count. Her appetite was fair, vomiting was very occasional, and her weight remained at 23 pounds. May 26 the following note was made: "Vaginal examination with colposcope shows no recurrence or persistence of the cancer noted at previous examination. The cervix is clean, slightly irregular, and there is a large white scarred area to the left of the cervix on the vaginal vault. Another is also noted in the right upper vagina, and to a lesser extent there is scarred tissue in the mid third of the vagina. The scar is coursed with fine blood vessels and is obviously the result of radium burns. At no place is there the slightest evidence of abnormal tissue."

On August 1 a slight blood stain was seen on the vulva, the first vaginal bleeding noted since February 1. Speculum examination on August 4 showed a small papillomatous-like nodule on the posterior lip of the cervix. This was removed for biopsy and reported as recurrent carcinoma of the cervix (S. P. 3908).

On September 17 a special size vaginal radium bomb was applied and 509 mc. hr. given. Following this treatment an ulcerative proctitis and bladder irritation developed, subsiding in approximately one and one-half weeks. Blood count on this admission was 4,810,000 red blood count and 82 per cent hemoglobin.

On September 23 vaginal speculum examination revealed no evidence of carcinomatous tissue. The vaginal vault was the site of an extensive white scarred area with new blood vessels running through the area of the radium scar. The nodule in the vault, found on August 4 previous to radiation, had completely disappeared, and the patient was discharged to return for a check-up in two months.

In November the child had tonsillitis, became asthenic, lost weight, and was occasionally constipated. Vaginal speculum examination November 23 was negative, but a rectal examination revealed a mass about the size of a lime in the cul-de-sac. A diagnosis of metastatic carcinoma was made and she was re-hospitalized.

On the fifth and last admission, Nov. 28, 1938, the child was twenty-one months old. The blood count at this time showed 4,380,000 red blood cells and 75 per cent hemoglobin. The course from this point was progressively downhill. She had a foul-smelling, thick, mucoid, vaginal discharge on admission and soon developed

excoriation of the perineal and rectal region. Six days after admission edema of the left leg was noted and this became more marked each day. A very definite change for the worse was evident on December 18. There was marked dyspnea, anorexia, and the face and extremities took on a bluish pallor.

An abdominal mass was palpated reaching the level of the umbilicus. The anus was distended and the mass filled the pelvis and lower abdomen. Signs of definite pneumonic process were present, confirmed by x-ray, due to real pneumonia or metastatic involvement. The child's pulse became imperceptible, her temperature rose to 104° F. plus and she died Dec. 20, 1938, aged 1 year 10 months.

*Autopsy.*—*Gross:* Body was that of a female infant, weighing 20 kilograms and measuring 84 cm. in length. It was markedly emaciated. The chief findings were in the pelvic cavity which was filled by nodular hard masses partly extending above the pelvic brim posteriorly. Abdominal wall showed no remnant of the transplanted ovary. In the chest retromediastinal masses were found about 6 cm. in diameter, compressing the esophagus and trachea, and pushing the aorta to the left. Numerous hard lymph nodes 1 to 2 cm. in diameter surrounded the primary bronchi. Both lungs, particularly the right lower lobe, were filled with tumor masses, showing large areas of necrosis. Pelvic organs had to be removed in toto. Only a small portion of the fundus showed normal outlines. The rest of the uterus and the upper portion of the vagina were replaced by fibrous gray growth, invading both the parametria, anteriorly penetrating the bladder and forming a small warty growth over the lower surface of the bladder mucosa. Posteriorly the growth had invaded the rectum, and compressed both ureters and both kidneys. Both kidneys were cystic and on cross section, distended caseous areas were seen containing turbid fluid. The liver weighed 337 Gm., had greenish parenchyma and was studded with smaller and larger nodules varying from 2 mm. to 3 cm.

*Anatomic Diagnosis:* Carcinoma of cervix uteri with extension to parametria, bladder, and rectum. Metastases to retroperitoneal and mediastinal lymph nodes, lungs, and liver.

*Microscopic section* of the primary mass and metastases showed identical appearance, with a glandular growth of low cuboidal cells showing marked anaplasia and very numerous mitotic figures.

*Microscopic Diagnosis:* Adenocarcinoma of cervix uteri with metastases.

I wish to express my thanks to Dr. J. Heilbrun, to whom the bleeding was first reported and who referred the patient to me; to Dr. J. Faison and his associates, who provided and applied the special radium applicators, and to Dr. N. M. Alter, who followed most avidly the pathologic changes and developments.

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The author analyzes the results obtained in a series of 253 hysterosalpingographies. There was 1.6 per cent higher incidence of closed tubes when the test was carried out during the premenstrual period. Pre-existing pelvic infection was reactivated in 7 women in spite of careful observation of the contraindications to the test. A group of six women in whom tubal implantation had been performed, were followed roentgenologically over long periods. In 5 the tubes remained patent and two of these had successful pregnancies following reimplantation. Bilateral tubal occlusion was found in 30 per cent of the 60 women with primary sterility and in 48 women with relative sterility. Tubal pathology was found in 49 per cent of 94 women with other gynecologic complaints; almost half of these showed bilateral tubal occlusion.

In grouping the entire series, 27 per cent showed bilateral tubal occlusion. These could be explained on the following basis: 14.6 per cent followed a febrile puerperium, 26 per cent followed abortion, 18 per cent were nonspecific in origin, 13 per cent followed gonorrheal infections, and 9.8 per cent were secondary to appendicitis.

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# ACUTE ANTERIOR POLIOMYELITIS COMPLICATING CARCINOMA OF THE CERVIX IN A THIRTY-YEAR-OLD FEMALE

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(From the Communicable Disease and Gynecological Services,  
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W S., a 30-year-old white female, was admitted to the Kingston Avenue Hospital on Oct. 6, 1939, complaining of inability to move both lower extremities. Her family history was irrelevant except that her mother died in her early forties of cancer. Menstruation began at the age of sixteen and was irregular, moderate in amount and of 4 to 5 days' duration. She had one child, seven years old, delivered spontaneously. Two induced abortions preceded her delivery in the space of two years. Her past history dates back to October, 1937, at which time she noticed spotting between her otherwise normal menstrual periods. The bleeding gradually increased in intensity. After three months she consulted a private physician who diagnosed a tubal pregnancy and gave her heat therapy for one month. The metrorrhagia continued and the patient, during the following year, consulted many physicians who recommended various medications. In September, 1938, the patient had a profuse vaginal hemorrhage. This was controlled by packing. The following month she entered a local hospital where a pelvic examination revealed a slightly enlarged uterus, induration of the left parametrium, and a deep excoriating ulcer over the anterior cervical lip. Clinical diagnosis was carcinoma of the cervix, Schmitz III. A biopsy of this ulcer revealed it to be carcinomatous. She entered the Brooklyn Cancer Institute November 3, 1938.

The physical examination was essentially negative except for the pelvic findings. A repeated biopsy of the cervix on Nov. 5, 1938, revealed a transitional cell carcinoma. Urinalysis and blood Wassermann were negative. Blood count revealed a mild secondary anemia. Roentgenography showed no evidence of pulmonary or cardiac pathology or osseous metastasis.

Between Nov. 7, 1938, and Feb. 8, 1939, the patient received a course of deep x-ray therapy of the following factors: 6 pelvic ports (2 anterior, 2 lateral and 2 posterior), 10 by 15 cm., 200 KV, 2 mm. cu. + 1 mm. AL, 50 cm. T.S.D.; 200 r. to 3 areas daily, total 2,400 r. each. Between Feb. 9, 1939, and Feb. 24, 1939, an intravaginal port of contact therapy was given (all factors as above) 400 r. units daily for a total of 4,000 r.

On Jan. 6, 1939, because of continued vaginal bleeding, despite the roentgen therapy, watery discharge and pain in the back which radiated to the left hip and leg, the patient was readmitted to the Brooklyn Cancer Institute. Pelvic examination revealed a slightly enlarged uterus and a moderately hypertrophied cervix. The anterior cervical lip was the seat of a deep ulcer, which was the site of the bleeding. Vaginal as well as rectal examination revealed a dense parametrial infiltration on the left. Biopsy of the cervix on Jan. 20, 1939, still showed a squamous cell carcinoma.

On Jan. 20, 1939, the patient received 3,000 mg. hr. of radium element by means of a tandem, colpostat and cork inserted into the cervix and vagina. Ten days later, an additional 2,000 mg. hr. was administered by the same technique. On Sept. 11, 1939, the patient weighed 116 pounds, a gain of 10 pounds in seven months.

On Sept. 15, 1939, the patient contracted a cold, had malaise the following day, and improved somewhat during the next two days. The following day the temperature rose again, the patient vomited several times, the headache became

jections of testosterone,<sup>5</sup> but this may occur similarly with estrone.<sup>6</sup> On the other hand the response of the myometrium seems fairly clear. Estrone will initiate and maintain rhythmic, intermittent contractility. Testosterone will inhibit this.<sup>7</sup> Since the myometrium plays such an essential role in controlling the volume flow of blood to the endometrium,<sup>8, 9</sup> the effect of testosterone on it becomes the more significant. Because intermittent, rhythmic motility is inhibited, the volume flow of blood to the uterus is lessened.<sup>10</sup> By reason of its direct squeezing action on the myometrial elements,<sup>1</sup> the volume flow of blood in the myometrium is reduced. The end result will be a reduction in the flow of blood to the endometrium, and thus, a diminution in the amount of uterine bleeding.

#### MATERIAL

On the basis outlined above, and remembering the well-known clinical fact that patients with arrhenoblastomas experience first a diminution and then a cessation of menses, we began more than a year ago to observe and treat patients with metromenorrhagia with testosterone propionate. Some were carefully followed for some months before being treated. Since the immediate treatment of the bleeding is the primary concern of this report, we have selected 14 typical cases. All but 2 have had at least 1 previous dilatation and curettage. Their ages ranged from 15 to 48 years.

Endometrial findings were as follows: hyperplasia, 6; secretory, 3; interval, non-secretory, 7; and chronic endometritis, 1. This makes a total of 17, because 3 patients presented a different type of endometrium on separate occasions of profuse bleeding. One showed hyperplasia on 2 occasions and an interval, nonsecretory phase on another. Two showed a secretory endometrium at one time and an interval, non-secretory picture on a subsequent curettage. A previous history of pelvic inflammatory disease was given by 4, of which 2 had endometrial hyperplasia; 1 an interval, nonsecretory endometrium, and 1, chronic endometritis. Two dated their excessive bleeding from parturition; 1 had hyperplasia, and the other showed a secretory endometrium on one occasion and an interval, nonsecretory picture subsequently. There were 2 cases of puberty menorrhagia, both hyperplasia; and 3 premenopausal, 1 hyperplasia, and 2 interval, nonsecretory.

#### DOSAGE

The dosage employed at any one time ranged from 5 to 25 mg. of testosterone propionate. The usual dose was 10 mg. Where the bleeding was active and quite profuse, the first dose was given either intramuscularly or else divided between the intramuscular and subcutaneous routes, the subsequent injections being given subcutaneously. When given by the latter route, the hormone was injected deep enough so that no swelling was apparent in the skin over the deltoid region. An intravenous needle was used.

The interval between injections varied from two to four days. As a rule 2 to 4 injections were sufficient. The average minimal dosage necessary to lessen bleeding materially was 10 to 30 mg. The total dosage required to stop the flow completely varied from 10 to 120 mg., with an average of 40 to 60 mg.

The elapsed time before a therapeutic result was obvious varied from twelve hours to four days. Usually there was a sharp diminution in bleeding within forty-eight hours.

When used prophylactically, the dosage varies somewhat with the type of endometrium found premenstrually. In cases with a secretory or an interval, non-secretory picture, a total of 10 to 30 mg. of testosterone propionate given in divided doses, subcutaneously, in the seven to ten days before the expected period is usually sufficient to control the succeeding period. In cases of hyperplasia, 50 to 100 mg. given in divided subcutaneous doses during the last two or three weeks of the cycle usually check the tendency to excessive flow.

## SUMMARY

A case of acute anterior poliomyelitis complicating carcinoma of the cervix in a 30-year-old female patient is presented. The important features of the differential diagnosis of these two entities are stressed.

## COMMENT

This case is of special interest because of the unusual finding of poliomyelitis in association with carcinoma of the cervix. Poliomyelitis in adults is very rare. The incidence was 0.6 per cent of the reported cases during the 1931 epidemic in New York City. The diagnosis of poliomyelitis was delayed in this case because a carcinomatous metastasis to the spine appeared to be a more likely possibility, especially in view of the pathologic diagnosis of carcinoma of the cervix following biopsy and the presence of paralysis, atrophy, and neurogenic bladder. However, the complications of a carcinoma of the cervix are usually those of induration and infiltration of the parametrium implicating the ureters and leading inevitably to a progressive and fatal hydronephrosis. Second, metastasis of carcinoma of the cervix to the skeletal system is quite rare. As far as can be ascertained in the literature, neurogenic bladder due to a metastasis of carcinoma of the cervix seldom occurs. The fact that the paralysis developed in an acutely ill patient who presented signs of meningeal irritation accompanied by characteristic changes in the cerebrospinal fluid, in addition to the involvement of scattered muscle groups and absence of sensory changes, was significant enough to have invited the suspicion that these were manifestations of a condition arising *de novo*. Moreover, the onset of this clinical picture coincided closely with the height of the seasonal incidence of poliomyelitis.

600 ALBANY AVENUE

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## UNFAVORABLE SULFANILAMIDE REACTION AND BLEEDING DUODENAL ULCER COMPLICATING A PUERPERIUM

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*(From the Obstetrical Departments of the Endicott-Johnson Medical  
Service and Ideal Hospital)*

**T**HIS case is reported because of the unusual picture of a severe gastrointestinal hemorrhage in the puerperium already complicated by pyelitis and an unfavorable sulfanilamide reaction.

V. M. (No. 31465), aged 39 years, gravida viii, para vii, was admitted to Ideal Hospital at 6:50 P.M. Dec. 2, 1939. A previous history is inadequate because of a very marked speech defect, but a subsequent study of the record showed nothing abnormal during the ante-partum course. The patient's blood pressure, blood count, and urine were normal eleven days prior to admission. Medical histories were located and studied back as far as 1934. They showed only a number of minor medical complaints and a history of one severe pyelitis in 1934 which required hospitalization. In these records there was no mention of gastrointestinal complaints or disturbances of any type. On admission, the patient had slight irregular contractions for twelve hours and developed a very marked abdominal distention. A physical examination showed a vertex presenting, fetal heart good, blood pressure normal. The pains became more frequent but were of poor quality. The patient was unable to void at any time. At 9:25 A.M. a catheterized specimen showed four-plus albumin and free blood and a culture was reported as loaded with *B. coli*. Labor progressed very slowly. The pains were irregular and of very poor quality although the patient complained bitterly both during and between contraction. Labor was terminated by low forceps shortly after full dilatation. Only moderate

severe, and the patient complained of pain in the left knee. Within the next twenty-four hours she developed a stiff neck and a rigid back; the next day a progressive weakness of the left leg appeared. The patient's condition at that time was diagnosed as "grippe." On Sept. 22, 1939, there was clinical evidence of paresis of the right leg. On Sept. 24, 1939, the patient was admitted to Kings County Hospital. The temperature on admission was 100° F., pulse 118, respirations 22, and blood pressure 110/60. The following day a neurologic consultation reported: "There is a symmetrical flaccid paraplegia, left worse than right. There is weakness of the hip, knee, and ankle. Deep reflexes are not elicited. There is no response to plantar stimulation. Abdominals are intact. Sensation is entirely intact, including the saddle. Impression: findings are those of a purely motor disturbance of the lower motor neuron type. The symmetrical character as well as the absence of sensory changes would suggest intraspinal disease, the actual nature or location of which is not clear. It would be difficult to understand how a localized metastatic disease of the spine could give such extensive involvement and yet not produce sensory changes or pain. Involvement of the cauda equina must be ruled out."

On Sept. 26, 1939, it was noted that the patient had not voided for the past twenty-four hours, which suggested the presence of a neurogenic bladder. On Sept. 28, 1939, the patient was transferred to the Brooklyn Cancer Institute where the same findings were noted. A lumbar puncture was performed which revealed the following: Clear fluid under normal pressure with no evidence of intrathecal block. Qualitative globulin was 2-plus, chlorides 705 mg. The Kahn and Wassermann tests were negative. The blood chemistry findings were normal, while the count showed a mild anemia. Urinalysis revealed a faint trace of albumin, 3 to 4 white blood cells per high power field. Roentgenograms of the skull and spine revealed no metastatic or other osseous lesions.

At this stage, the diagnosis of poliomyelitis was entertained and on Oct. 6, 1939, the patient was transferred to the Kingston Avenue Hospital, where physical examination revealed a fairly well-nourished adult female, complaining of pain in the left hip and thigh. The right lower extremity showed partial loss of power of the hip flexors, the quadriceps, and the calf muscles. The left lower extremity was completely flaccid with moderate atrophy. The spinal musculature was weak. There were no sensory changes. Deep reflexes of both lower extremities were absent. A spinal tap was productive of crystal clear fluid under normal pressure, with no evidence of block. There were 25 cells (all lymphocytes) per c.mm. Total protein was 78 mg. per cent; chlorides, 665 mg. per cent; sugar, 59 mg. per cent. There was a faint trace of globulin. No organisms were cultured. Pelvic examination: the vagina showed conical atresia with the fornices obliterated, the cervix was small, smooth, firm and partially fixed. The uterus and adnexa were atrophic (postradiation). Rectal examination showed moderate bilateral parametrial infiltration. The course in the hospital was uneventful and afebrile. Posterior plaster-of-Paris splints were applied to both lower extremities, and, on the eighth day of hospitalization, the patient was transferred to the orthopedic division of Kings County Hospital for physiotherapy.

Further examination revealed that the entire left lower limb was flaccid. There was almost complete paralysis except for the tensor fascia lata which still retained approximately half of its normal function. The right lower extremities showed major involvement of hip flexors, hip adductors, quadriceps, hamstrings and posterior tibial; all other muscles were involved to a minor degree. Removable splints were applied and hydrotherapy was instituted for a period of three months. Baking and massage with gentle passive exercise were later employed. Patient was confined to bed throughout with fixation supportive splints in situ. After this time, the left limb was still flail and the right limb had recovered muscle function from -3\* to -1 in all groups. Reflexes remained absent. Atrophy of the left lower limb was one inch greater than the right.

\*-4 equals loss of all power.

-3 equals loss of  $\frac{3}{4}$  power.

-2 equals loss of  $\frac{1}{2}$  power.

-1 equals loss of  $\frac{1}{4}$  power.

was that it resulted from immediate manual manipulation. It was, however, possible that the infection which appeared to be a descending one, had previously perforated the vaginal wall, either with or without a distinct opening. Roughened areas of endometrium were present in the upper portion of the uterine cavity. This tissue appeared necrotic and discolored and was connected with the vagina by injected streaks along the endometrium. The remainder of the endometrium was not remarkable and grossly showed no evidence of being involved in the infectious process. The uterine wall, while boggy, showed no visible evidence of being infected on sectioning.

Microscopic examination showed:

*Lungs:* The sections showed the presence of an acute bronchopneumonia associated with marked edema of the lung tissue and engorgement of blood vessels, large and small. Microscopically, the picture was that of a terminal hypostatic bilateral pneumonitis.

*Gastrointestinal Tract:* Duodenum sections showed an ulceration in the mucosa which had excavated down to the submucosa. The base of the ulcer was necrotic and hemorrhagic. An active inflammatory reaction associated with the ulcer was exhibited by a diffuse infiltration of the duodenal wall by eosinophiles and lymphocytes. The wall was also markedly edematous. The serosal aspect of the duodenum was actively inflamed. Sections from other portions of the intestinal tract showed necrosis of the superficial aspects of the mucosa and a marked diffuse inflammatory reaction throughout the submucosa, muscularis, and adventitia.

*Kidneys:* The right kidney showed a moderate pyelonephritis. This was shown by foci of both acute and chronic inflammatory cells in the kidney which were present in various parts of cortex, medulla, and renal pelvis. In these areas, destruction and fibrous replacement of glomeruli had taken place; tubules were damaged and contained necrotic debris and bacteria. The damage was moderate in degree, as much of the kidney revealed only parenchymatous degeneration and edema. In the ordinary case of this sort it was possible to consider the infectious process as an ascending one. In this case, the picture was complicated by the fact that the perirenal tissues, which were markedly actively inflamed, communicated through a break in the kidney capsule with the most actively inflamed areas within the kidney. One could surmise without settling the question definitely that infection entered the kidney from without, or on the other hand, that infection originated within the kidney and involved the capsule secondarily, or still further, that the two processes started independently and joined forces. The most alluring one to me as I review the evidence is that an infection originated in the duodenal ulcer and spread from there to the kidney and also down the psoas to the pelvis.

*Uterus:* The roughened area of the uterine cavity microscopically was seen to be the seat of distended venous sinuses filled with clot, associated with atrophic and necrotic endometrium. There was evidence of moderate acute inflammation in the area. The uterine musculature underlying this area was loose and edematous but apparently free from infection. The cervical tissues and the vaginal wall were necrotic and very acutely inflamed. It seemed inevitable that the poorly nourished endometrium should become infected, but the condition of the uterine wall and the remainder of the endometrium indicated that the process was incidental and secondary and not a primary source of the pelvic and other pathology.

#### CONCLUSION

After studying the history and seeing the autopsy, I feel that here the pregnancy was incidental to two underlying conditions: namely, pyelitis and duodenal ulcer. The duodenal ulcer hemorrhage plus the unfavorable reaction to sulfanilamide were a most unfortunate combination and were definitely contributory to her death. Sulfanilamide, although a great advance in therapy, is a drug to be used only with caution and the blood count must be followed very closely throughout its administration.

This case illustrates the well-known, but often forgotten fact that pregnant women do suffer from any and all medical complications.

traction was used. About 50 c.c. amniotic fluid stained with dark red blood followed delivery. There was a fetal heartbeat but no respiratory response to use of stimulants or resuscitator. The placenta did not show any definite location of premature separation. Autopsy of the infant showed a large subcapsular hemorrhage on the inferior surface of the liver and a diffuse hemorrhage into the right adrenal gland. The puerperium was stormy throughout.

The first three days there was marked abdominal distention with some right flank tenderness. Temperature 100° to 101° F., pulse 130 to 140. On the fourth day the patient passed a copious tarry stool. The red count was 3,620,000, Hg, 65 per cent; white count, 11,050; and polymorphonuclears, 90 per cent. Sulfanilamide was started. The next two days there were frequent large intestinal hemorrhages. Transfusions were given daily, yet the red count was down to 1,970,000. Eighty grains of sulfanilamide had been given over a period of forty hours and a check on the white count showed a drop from 11,050 to 4,100. The polymorphonuclears went down to 40 per cent. The patient's general condition was decidedly worse. Because of the subcapsular and adrenal hemorrhages in the infant, the possibility of a blood dyscrasia was considered. Bleeding and clotting time, clot retraction time, fragility test, and prothrombin content were all within normal limits. Transfusions were continued but on the eighth day post partum bronchopneumonia developed and the patient died. Shortly before death, the red count was 1,860,000; Hg, 47 per cent; white count, 1,850; polymorphonuclears, 60 per cent.

The essential parts of the autopsy report are:

*Peritoneal Cavity:* The most important feature presenting itself was a marked gangrene of the retroperitoneal tissues.

*Heart:* This organ appeared of normal size but was very soft and flabby. The subcardial fat was moderate in amount. The coronary arteries appeared patent and free from visible degeneration. The mitral valves showed definite, healed fibrous thickenings along the line of closure. The other valves were not remarkable. The myocardium was uniform in color and consistency, being of a dull brownish color and soft.

*Lungs:* The lungs showed indication of consolidation throughout all lobes. The picture, most pronounced in the lower lobes, was that of a bilateral pneumonitis.

*Spleen:* Grossly, the picture was that of a marked toxic splenitis and passive congestion.

*Gastrointestinal Tract:* Duodenal ulcer. No obstruction was found throughout the length of this tract. The extreme gaseous distention without obstruction from feces or abnormality of wall indicated paralytic ileus. The stomach was negative. A definite pear-shaped, shallow ulceration was noted in the duodenum about 1 cm. distal to the pyloric sphincter. The ulceration was about 8 mm. long and half as wide. The duodenal mucosa was congested for a considerable distance beyond the ulceration. An examination of the mucosa throughout the rest of the tract showed no features of interest grossly.

*Liver:* A marked degree of parenchymatous degeneration was indicated together with toxic hepatitis.

*Kidneys:* Weights: each weighed 227 Gm. The capsule of each stripped clean but not easily. The surfaces revealed were pale and smooth and mottled by fine grayish, closely set foci. The cut surfaces of each were similar and showed a corticomedullary portion narrower than normal, due to distinct and fairly marked pelvic dilatations characteristic of moderate hydronephrosis. The kidney cut surfaces were paler than normal with some slight indistinctness of the architectural markings suggestive of inflammatory change.

*Ureters:* The lower portions of each ureter were lost in the mass of necrotic tissue in the pelvis and were not traced.

*Bladder:* On section it gave the impression of acute cystitis.

*Genitalia:* The uterine cervix was deeply congested, red in color and swollen, features which also characterized the entire vaginal mucosa with which it blended. A rent in the friable vaginal wall on the right side was noted after removal. Because of the friability of the vaginal tissue and because this opening was not noted during preliminary examination of the vagina and uterus in situ, the assumption



smaller piece of cystic ovary is also submitted. Normal appearing appendix 6 cm. long. Microscopic: The hemorrhagic mass from the ovary consists of old blood clot adjacent to ovarian tissue. The section indicates that the blood clot is adherent to the ovary rather than having originated within the organ. Numerous amorphous, blue staining masses have the appearance of necrotic chorionic villi, but no decidual cells are recognizable. *Diagnosis:* Suggests ectopic pregnancy." Following this report further sections were studied and in one a villus was found that seemed to be attached to ovarian stroma (see Fig. 1).



Fig. 1.—Photomicrograph showing villus apparently attached to ovarian stroma. Shadows of degenerating villi were found in the blood clot that made up a considerable part of the ovarian mass.

Our final diagnosis in this case was ovarian pregnancy with death of the embryo and beginning absorption of the products of conception. Whether this was a primary or a secondary ovarian pregnancy cannot be determined. It is possible that this patient had a tubal abortion at the time of her abdominal distress on the night of June 1, the early fertilized ovum becoming attached to the ovary at the site of rupture of the follicle from which the egg escaped. The two positive Friedman tests, on June 13 and July 24, indicate that embryonic development must have continued for at least two months. Death of the embryo may have resulted from an inadequate blood supply. Our findings at the time of operation suggest a gradual absorption of the products of conception and if the operation had been delayed several weeks longer, it is possible that no evidence of the pregnancy would have been found. The findings in this case suggest that an ovarian pregnancy may be missed very easily.

Fortunately this patient became pregnant again early in July, 1939, and she apparently has a normal intrauterine pregnancy.

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Nogues, A. E., and Gazzotti, C. L.: Mammography, *Rev. méd. latino-am.* 24: 999, 1939.

The technique and difficulties of mammography are described by Nogues and Gazzotti. They used colloidal thorium dioxide. No unfavorable reactions were traceable to the injections. Mammography has an important place in the diagnosis of intracanalicular tumors as well as being of localizing value for any processes involving the ducts. It is an important adjunct test in paracanalicular tumors. It should be used routinely in all cases of abnormal nipple secretions not amenable to usual treatment. An excellent series of radiographs is presented.

R. J. WEISSMAN.

## FRIEDMAN TESTS WITH OVARIAN PREGNANCY\*

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OVARIAN pregnancies are sufficiently rare to warrant reporting each case history. The case to be reported is of special interest, owing to a record of two positive Friedman tests during the first two months of pregnancy followed by a negative test shortly before surgery was advised.

Mrs. E. G., aged 25 years, consulted one of us (V. S.) on June 3, 1938, at which time she gave a history of a sudden severe pain in the lower abdomen on the night of June 1, at a time when her menstrual period was overdue two weeks. Her menstrual periods began at the age of 14 years and had been regular twenty-eight-day type, lasting four days, usually without pain. She had been married five years and the only period she could recall missing in the past had been in September, 1937. Her past medical history was negative except for measles, mumps, and scarlet fever as a child, and she had passed a urinary calculus in 1935 after several attacks of renal colic. The attack of pain on the night of June 1 was severe, and at its onset she felt faint and was unable to lie flat without an exaggeration of the distress. However, it gradually disappeared, a physician's services not being secured, and she came for an examination to determine if she was pregnant. The general examination was essentially negative except for an unusual growth of hair on her body and a male type of distribution on her abdomen. The external genitals were negative. On bimanual examination the uterus was found to be retroverted, slightly enlarged, and softer than normal. The left adnexa seemed normal, while the right appeared to be adherent to the side of the uterus. Pregnancy was suspected but a definite diagnosis could not be made. The patient was very anxious to know whether or not she was pregnant and a week later when it was still impossible to make a definite diagnosis a Friedman test was advised. This test was reported positive on June 13. On July 20, she reported that there had been some irregular bleeding during the past two weeks. Daily injections of progesterin were given for ten days. On July 26 another Friedman test was reported positive. However, she had only short intervals of freedom from an offensive, red vaginal discharge which lasted about five weeks. Bimanual examinations on August 22 and September 12 showed that the uterus was not enlarging normally. On September 24 she reported that after freedom from discharge for four weeks there had been five days of what seemed to be a normal menstrual flow. Bimanual examination at this time showed no evidence of uterine enlargement, but there was a tender mass at the right side of the uterus. A Friedman test was reported negative on September 27. It was believed that she had a right-sided ectopic pregnancy, but the possibility of an ovarian neoplasm was considered. Surgery was advised. On opening the abdomen on October 6, both tubes appeared normal, but both ovaries were enlarged and adherent. The larger right ovary was 5.5 cm. in diameter and its appearance suggested endometriosis. The left ovary while smaller was cystic and adherent to the pelvic wall. The right ovary was removed and the left ovary resected. A grossly normal appendix was removed by request. At the time of the operation, it was believed that she must have had a uterine abortion during July or the first days of August, and that she had an endometriosis of the right ovary.

The report of the pathologist was as follows: "Gross: Ovary enlarged to a diameter of 5.5 cm. by a dull red mass resembling old blood clot. A second

\*Presented at a meeting of the Obstetrical Society of Philadelphia, January 4, 1940.

times a day to control bleeding started active bleeding from the intact anterior vaginal vault. Packing was stopped on December 18, and kephrine hydrochloride (methyldaminoacetatechol hydrochloride) was blown into the vagina by means of a Wyeth blower. The powder was applied from one to six times daily (as often as bleeding appeared). Within six days after the use of this powder, the bleeding practically ceased. By January 4, two months from the onset of hemorrhage, the bleeding stopped completely. At this time the hemoglobin was 60 per cent (Sahli), and the red blood count was 3,600,000.

During these two months the patient had been given sixteen blood transfusions varying from 500 to 700 c.c. of whole blood. On February 5, three months from the onset, the patient was discharged from the hospital after being up and about for two weeks. Three days after leaving the hospital she developed a large ecchymotic area extending from the right hand to the elbow. There was no history of injury. On February 15, the patient was admitted to Mount Sinai Hospital for blood studies. The outstanding findings were clotting time, 75 to 100 minutes, and prothrombin time eight times greater than normal. Subsequently the patient developed ecchymotic areas on the legs as well as the abdomen. The last week in February the patient had what she described as a normal menstrual period lasting four days. On March 4, two months after all bleeding had ceased, the vaginal mucosa was inspected, was found to be well healed, and the silk sutures were removed. The patient was up and about and doing her usual household duties but continued to develop spontaneous ecchymotic areas on different parts of her body.

On April 20th a blood study was made by Dr. Gurth Carpenter, of the University of Chicago. The platelet count was 290,000, clotting time one and three quarter minutes, bleeding time two minutes, red blood count 4,880,000, normal white and differential counts. In his report Dr. Carpenter stated: "I emphasize the fact that our investigations were not complete on the basis of one visit. It is my impression that this case belongs to that ill-defined, poorly described bleeding tendencies associated with endocrine dyscrasias." This blood picture was obtained nine days prior to the death of the patient.

On April 29 she entered Mount Sinai Hospital with the history of having been bitten on the tongue. The tongue was found to be tremendously swollen and occupied the entire oral cavity. A tongue depressor could not be inserted between the tongue and the roof of the mouth. The tongue was blue red in color, and there were clots of blood in the oral cavity. The submental, submaxillary and thyroid areas showed hemorrhagic distention of the underlying structures. The patient had marked dyspnea, requiring use of the accessory muscles of respiration. A tracheotomy was done by Dr. M. R. Guttman to relieve the respiratory embarrassment. The patient's condition remained good for about six hours after the tracheotomy. This was followed by sudden massive hemorrhage and the patient literally drowned in her own blood. No autopsy was obtained.

### CONCLUSIONS

In view of the patient's history, the type of response to treatment, and the final outcome, it is believed that this patient must be placed into that group which has been classified as "constitutional capillary fragility."

### REFERENCE

- (1) *Leventhal, M. L., Lash, A. F., and Grossman, A.:* Surg. Gynec. Obst. 67: 102, 1938.

## HEMORRHAGE IN THE LATE PUERPERIUM\*

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**H**EMORRHAGE in the late puerperium is usually pelvic in origin and rarely due to a blood dyscrasia. The presence of such a true blood dyscrasia usually manifests itself during labor and/or the immediate puerperium. Delayed manifestations resulting from such a dyscrasia are sufficiently uncommon to warrant the following report.

The patient, A. W., a white, 26-year-old primigravida, at term, was admitted to the Michael Reese Hospital in the first stage of labor on Oct. 19, 1938. Her pregnancy had been uneventful, the Wassermann test negative, and there was nothing in her history or physical findings suggestive of blood dyscrasia.

After thirty-six hours of labor, the heart tones, which had been 160, became somewhat irregular and dropped to 116-128. Cervical dilatation at this time was 7 cm. with the head at the level of the ischial spines. An hour later the heart tones became very irregular and slow, and it was therefore decided to terminate labor. Dührssen's incisions of the cervix were made at "two" and "ten o'clock," a deep mediolateral episiotomy was done, and the fetus extracted by midforceps. A right sulcus tear resulted which was repaired together with the Dührssen's incisions and the episiotomy. The patient made an uneventful recovery. She was out of bed on the eighth day and left the hospital on the eleventh day.

Three days after discharge from the hospital the patient began to bleed vaginally. Speculum examination revealed the cervix well healed with no evidence of bleeding from the canal. The impression at this time was that of delayed post-partum hemorrhage. Two days later the bleeding became profuse. A curettage was done, and a small amount of decidual tissue was removed. No placental tissue was found. Five days after the curettage, profuse bleeding recurred. Speculum examination now revealed bleeding from a pin-point area in the suture line of the right sulcus tear. This was located in the middle third of the vagina. The suture line had healed by primary union, and there was no sign of infection. No evidence of the suture line other than that similar to a scratch made by a pinhead on the skin could be seen.

Between November 16 and December 14 (fifth to ninth week post partum), this vaginal mucosa was sutured five different times for recurrent bleeding, using both catgut and silk. The ligatures controlled the bleeding from two to five days. Vaginal packing was used in the intervals between the various ligations, and when the patient lost blood faster than transfusions could replace it, resuturing was done. On occasion two transfusions of 500 c.c. of whole blood were given in a single day. On November 30, twenty-three days from the initial bleeding, the clotting time was prolonged for the first time from one and one-half to nine minutes. On December 3, the right internal iliac artery was ligated through an extraperitoneal approach.<sup>1</sup> Bleeding was decreased for only eight hours. On December 4, bleeding was again out of control and the left internal iliac artery was ligated. On December 6 the red blood count had dropped to 1,360,000, the platelets were 150,000, clotting time was ten minutes, and bleeding time was twelve minutes. Although the bleeding was not stopped, it had decreased markedly and was under control after ligation of both internal iliac arteries. Five days after the right ligation a large hematoma appeared in the right inguinal wound. On December 14, consultation with Dr. S. O. Schwartz, hematologist at Michael Reese Hospital, brought forth the suggestion that constitutional capillary fragility was a factor in the bleeding. Moccasin snake venom was therefore used, being administered subcutaneously. On December 15, blood standing for twenty-four hours did not coagulate. A large hematoma now appeared in the left inguinal incision (fourteen days post-operative). The irritation from constant changing of cotton packing one to two

\*Presented at a meeting of the Chicago Gynecological Society, January 19, 1940.

the vagina, a polypoid tumor was found attached to the cervix. This tumor was about three inches long and about an inch in diameter at the largest point. No tubal opening was apparent, and it was felt that we were dealing with a fibroid. An attempt was made to snare this tumor off, but the snare would not cut through it. The cavity of the uterus was definitely made out on the right side.

Very little bleeding occurred after removal of the tumor, but a light pack was inserted up to the operative wound.

The pathologist reported that the ovary, tube, and uterus had been removed.

I have no idea when the inversion of the uterus occurred. It would have been impossible to have replaced this uterus without incising it longitudinally, as complete involution had taken place with the uterus in the inverted position.

A most interesting fact was the absence of bleeding from the cut uterine and ovarian arteries, and the total absence of shock from the inversion of the uterus.

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## ECLAMPSIA ASSOCIATED WITH PLACENTA PREVIA\*

FREDERICK A. WURZBACH, JR., B.S., M.D., NEW YORK, N. Y.

THE association of eclampsia and placenta previa is apparently a very rare obstetric condition. A review of the literature for the past forty years reveals only three reports. The first in 1904 is in an Italian journal not available in this country. The second is a report in 1910 by M. Plauchu of Lyon, France, where, because of oligohydramnios, he punctured through the placenta, draining the fluid, and, after dilatation was effected, did a craniotomy and extracted the child. This mother lived. The third case is one reported in 1921 by Douglas Miller, from the Royal Maternity Hospital, Edinburgh, of a postpartum eclampsia three days after a version and breech extraction for complete placenta previa. The mother and child both died.

### CASE REPORT

E. W., 25 years old, white, gravida ii, para 0, had a miscarriage at four months on Aug. 11, 1936. The last regular menstrual period occurred on Oct. 25, 1936; due date Aug. 2, 1937.

She was a regular attendant at the Pre-natal Clinic of Morrisania City Hospital from March 24, 1937, to June 9, 1937. At this last visit her blood pressure was 120/80. Her urine was negative and she had no complaints. The Wassermann and Kahn tests were negative. At 7:00 P.M. on the evening of June 21, 1937, her husband returned from work and found the patient lying on a couch in a pool of blood and in a comatose state. She was admitted from a public ambulance to our emergency room at 7:30 P.M.

On admission she was restless, irritable, and semistuporous. Almost immediately she had a generalized convulsion lasting several minutes. She was admitted to the open surgical ward under the care of the obstetric division. This was necessary as our wards were closed, and she was too critical to be again transported to any other hospital.

The past history was negative. The recent history revealed that for five days she had complained of headache, nausea, vomiting several times a day, puffiness of the face, and swelling of the ankles. She had not returned to the clinic and had relied on the self-administration of "headache powders."

Physical examination revealed a comatose patient in acute distress. Her face and eyelids were markedly edematous with a parchment feel to the skin. The pupils were widely dilated and reacted moderately to light. The eye grounds

\*Presented at a meeting of the Section of Obstetrics and Gynecology, New York Academy of Medicine, Feb. 27, 1940.

# INVERSION OF THE PREGNANT SIDE OF A DOUBLE UTERUS

LEROY E. BATES, M.D., SAN ANTONIO, TEX.

*(From the Gynecological and Obstetrical Service of the Santa Rosa Hospital)*

THE following case constitutes an unusual complication of pregnancy in a double uterus.

Mrs. C., aged 18 years, first came to me when she was six months pregnant. Her past history was uninteresting, except that she had had a previous spontaneous abortion at six weeks. All of her pelvic measurements were within normal range and a vaginal septum was discovered at the time of her first examination. It was thought that a bicornuate uterus was present. The pregnancy occurred in the left side as is usually the case when this anomaly is present.



Fig. 1.

She went into labor at seven months and delivered an apparently normally formed premature infant. Her delivery was remarkably easy, but the vaginal septum ruptured at the time. No difficulty was experienced with the delivery of the placenta. Traction was not exerted on the cord.

She did not lose an unusual quantity of blood at the time of her delivery and suffered absolutely no shock. For the first week her puerperium was entirely normal and she got out of bed on the eighth day. A day or two after she was up and around the house she began to bleed. She was put back to bed and given ergot for several days without any improvement.

Twenty-four days after delivery she was taken to the hospital with the intention of doing a curettage to control the bleeding. On inserting a speculum into

The following case histories briefly illustrate the method of approach:

CASE 1.—Patient, aged 39 years, had suffered with menorrhagia since parturition in 1936. A dilatation and curettage in 1937 revealed endometrial hyperplasia. She was seen on the eighteenth day of a profuse flow saturating 12 to 15 napkins daily. She was given 25 mg. of testosterone propionate intramuscularly. Two days later, the flow having abated considerably after a slight initial exacerbation the first night, she was given a similar dose. This was repeated twice. Total dosage was 100 mg. Two months later, she reported to the dispensary on the thirteenth day of another profuse flow. She was given 20 mg. of testosterone propionate subcutaneously and a similar dose was repeated six days later, the flow having become a dribble two days after the first injection. After that she was given 20 mg. subcutaneously twice a week for two weeks more. Since then (six months) her periods have been normal in duration and amount. It is to be noted that it required 100 mg. intramuscularly to stop the flow in five days while it required 40 mg. subcutaneously to stop it in eight days under essentially similar conditions.

CASE 2.—Patient, aged 29 years, had required a curettage for excessive menses twice in 1937. Both disclosed endometrial hyperplasia. Periods, however, continued to be profuse. Endometrial biopsy on the twenty-eighth day of the cycle revealed a very well-developed proliferative endometrium diagnosed as a questionable hyperplasia. She was given 30 mg. ( $3 \times 10$ ) in the next five days and then the period started as profuse as usual. She was given 10 mg. on the third day with no relief. On the sixth day, she was given 20 mg. intramuscularly. After an initial gush, the flow abruptly ceased that night. Sixty milligrams of testosterone propionate merely decreased the duration but not the amount of flow. Suction biopsy on the seventeenth day of the next cycle revealed an interval, nonsecretory endometrium. Starting on the twentieth day of the cycle she received 100 mg. of testosterone propionate in divided subcutaneous doses over the course of the next ten days. Suction biopsy on the thirty-first day revealed a secretory endometrium. Her period began on the thirty-fourth day, lasted four days, and was normal in amount. The finding of a secretory picture is probably explainable on the gonadotropic action of testosterone.<sup>16</sup> Suction biopsy two months later still showed a secretory endometrium premenstrually. When again seen six months later her only complaint was that she had still not regained her "nature" (libido), which had disappeared after the first series of injections. Her periods have continued to remain normal in duration and in amount.

CASE 3.—Patient, aged 23 years, colored housewife, had pelvic inflammatory disease in 1934. In the past two years she developed severe dysmenorrhea and polymenorrhea with profuse flow. For the past six months she complained of intermenstrual spotting. Pelvic examination revealed a normal but fixed, anteфлекed uterus. Endometrial biopsy on the day before her expected period disclosed an interval, nonsecretory picture. She was given 20 mg. ( $4 \times 5$ ) in the next eight days. Menses set in on the ninth day without pain, and was moderately profuse, requiring 7 to 8 pads daily instead of the usual 15 to 20 pads. Flow tapered off on the fifth day. However, it re-appeared on the seventh day along with menstrual cramps. Accordingly she was given 10 mg. intramuscularly. Following an increase of the flow that evening, menses stopped the next day. Endometrial biopsy a few months later showed a secretory picture premenstrually. Periods were normal in type, duration and amount (2 to 4 pads daily), while her dysmenorrhea had disappeared.

CASE 4.—This case illustrates the excellent results obtained in cases of cyclic menorrhagia from a secretory endometrium. Patient, aged 23 years, had cyclic menorrhagia for past seven years. Flow accompanied by clots, lasted nine to eleven days requiring 8 to 10 pads daily. Endometrial biopsy revealed a secretory phase premenstrually. She was given 15 mg. ( $3 \times 5$ ) in divided subcutaneous doses in the week before her period. Flow lasted but five days, contained no clots, and was normal in amount. Since then, with no further therapy, periods have been normal in duration and amount (six months).

showed a few old and new retinal hemorrhages, constricted arteries with indentations of the veins but no blurring of the disks. The ears, nose, and throat were normal. Her tongue was thick, swollen, beefy red and showed several fresh, bleeding wounds. The neck was not rigid. There was no cardiac pathology. The blood pressure (after the convulsive seizure) was 148/108, the pulse was 88 and the temperature 100.8° F. The lungs were clear throughout. The abdomen revealed an eight months' uterus, not ligneous and contracting occasionally. Fetal heart sounds could not be heard. There was much dried blood on the vulva and inner surfaces of her thighs. There was moderate edema of the forearms, hands, legs, and feet.

Immediate treatment was instituted for the eclampsia, consisting of 0.5 gr. of morphine sulphate stat and 0.25 gr. to be repeated every two hours as indicated, 50 c.c. of 50 per cent glucose and 30 c.c. of 10 per cent magnesium sulphate by vein. For the bleeding the foot of the bed was elevated, and there was immediate blood workup, typing and cross-matching of donors.

This treatment controlled the convulsions. Two hours after admission a vaginal examination was done with a donor ready. The vagina was found full of clots. The cervix was thick, soft, and one finger dilated. Placenta was felt covering the internal os. The head could be felt through the cervix anteriorly, and the placenta was believed to be for the most part on the posterior wall of the uterus. The membranes were intact. There was a continuous trickle of blood but no further massive hemorrhage.

The laboratory findings were red blood cells 5,500,000, hemoglobin 80 per cent. The husband was a compatible donor. The urine showed four-plus albumin, many fine and coarse granular casts, and many white blood cells. Urea nitrogen was 0.34 mg. per cent; sugar 75 mg. per cent.

The patient was in a desperate state and continued to bleed. It was believed that since the eclampsia was being controlled the best chance the patient would have for recovery would be a cesarean section, even though the fetus was dead. Three hours after admission a rapid classical section was performed and the dead fetus extracted. The placenta was found covering the internal os and posterior lower surface of the uterus. The uterus was packed and contracted well. Before and during the operation the patient received 700 c.c. of blood by citrate method.

Following the operation the patient had a stormy three days and required considerable stimulation by coramine and caffeine sodium benzoate. One-sixth grain of morphine sulphate and an ampoule of prostigmine every four hours were continued until the third day. One day after operation temperature was 101° F., the pulse 120, and blood pressure 138/74. The second day the temperature was 104° F., pulse 130, and blood pressure 190/138. Thereafter the temperature and pulse gradually fell and were normal by the seventh postoperative day. The edema was gone by the fourth day. The blood pressure receded slowly and was 120/90 on the tenth postoperative day. On discharge from the hospital on the twenty-eighth day, the wound was healed, her blood pressure was 126/88, and the urine still showed a trace of albumin, occasional red blood cells and white blood cells, and granular casts. The patient did not return for post-partum examination.

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## CANCER OF THE CERVIX IN A VIRGIN WITH INTACT HYMEN\*

A. F. LASH, PH.D., M.D., CHICAGO, ILL.

(From the Michael Reese and Cook County Hospitals)

THE occurrence of carcinoma of the cervix with uterine fibromyomas is well known, the incidence being 1 to 2.6 per cent according to various series of fibroid studies published. Mattmuller found 9.7 per cent of nulliparas among 442 patients with cancer of the cervix uteri of whom 10 or 2.2 per cent were virgins. On a study of over 2,000 specimens of uteri, cervixes, and curettings, Davidsohn found carcinoma of the cervix occurring in 0.93 per cent in Jewish women and 6.4 per cent in non-Jewish women.

This patient, A. S., a 40-year-old, unmarried, Jewish woman, entered the Michael Reese Hospital because of pressure and pain in the right lower quadrant, frequency of urination, nocturia, and menorrhagia. Her personal and past history contained nothing of significance, except that her menses began at the age of 13½ years, occurred every twenty-eight days, and remained for seven days, being profuse and associated with clots and some dysmenorrhea.



Fig. 1.—Adenocarcinoma of cervix with squamous cell features.

Physical examination showed a normal, small individual, weighing 109 pounds with no general pathology. Pelvic examination was made by recto-abdominal manual palpation because of a tight, intact hymen. The cervix was closed and smooth, the corpus was enlarged to the size of a twelve weeks' pregnancy, hard and free, and the adnexa presented no palpable pathology. A diagnosis was made of fibroids of the uterus.

On Jan. 11, 1939, I performed a subtotal hysterectomy and was surprised to find friable tissue in the endocervix on cutting across the cervix. Therefore, I removed the cervix and both tubes and ovaries. The patient made an uneventful recovery and was given a course of roentgenotherapy. The specimen showed multiple fibromyomas of the uterus with adenocarcinoma of the cervix with squamous cell features.

30 NORTH MICHIGAN AVENUE

\*Presented at a meeting of the Chicago Gynecological Society, January 19, 1940.

## A SILVER-PLATED VAGINAL PROSTHESIS FOR THE CONSTRUCTION OF AN ARTIFICIAL VAGINA\*

BUFORD WORD, M.D., BIRMINGHAM, ALA.

THIS instrument (Fig. 1) was made from the obturator of an old anoscope, being  $1\frac{1}{2}$  inches in diameter and  $4\frac{1}{2}$  inches in length. The instrument was made by cutting the flange off of the obturator, sealing the open end with a plug and welding on a button, as shown in Fig. 1. The prosthesis was then electroplated with pure silver  $\frac{3}{1,000}$  of an inch in thickness over the entire surface. In cases of congenital absence of the vagina, a cavity is created between the bladder and rectum and the

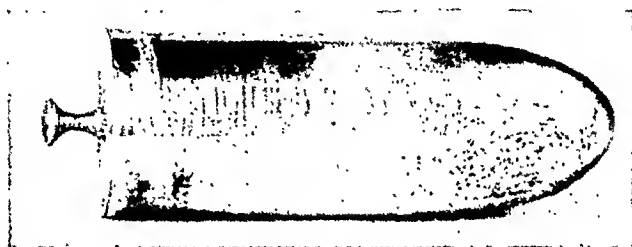


Fig. 1.



Fig. 2.

instrument inserted, to remain until epithelization of the cavity is complete. It may be removed any time after three weeks for inspection. Several pinch grafts of mucous membrane from the vestibule are recommended to be used on the end of the prosthesis to hasten growth of vaginal mucosa. Fig. 2 shows the instrument in place.

I have used the instrument in 4 cases, and it has worked very well. Silver is recognized as a bacteriostatic agent and is also helpful in promoting epithelial growth.

306 MEDICAL ARTS BUILDING

\*The above described instrument can be obtained from A. S. Aloe & Company, St. Louis, Mo.

## AN AUTOMATIC RECORDING APPARATUS FOR TUBAL INSUFFLATION\*

A. HERBERT MARBACH, M.D., PHILADELPHIA, PA.

(From the Obstetric and Gynecologic Service, Jewish Hospital)

MANY instruments have been used to facilitate Fallopian tubal insufflation, and, although all give us the required information, they lack the safety features which are desirable.

The use of compressed gas, coming from a tank into the instrument, has presented many difficulties. Chief among these was the use of a suitable reducing valve to prevent the high pressure in the tank from disrupting the outfit, necessitating many adjustments of the instrument before the test was able to be done. The recording devices in general use employ either a smoked drum or an inked stylus on kymograph paper. Such recordings have been of inestimable value in aiding diagnoses and instituting treatment.

A single dial recording instrument is presented herewith, which satisfies all of the desired and required qualifications for the proper completion of tubal insufflation. This device, in principle, eliminates errors, since personal adjustment is not necessary. The important considerations in devising the instrument were mechanical efficiency and safety, which in previous instruments have been lacking.

Carbon dioxide from the main supply tank is under 750 pounds pressure. By means of a safety control reducing valve, this pressure is cut down to 10 pounds before going to the patient. The rate of flow of the gas through this instrument is automatically regulated at 60 c.c. per minute, and with the instrument in operation, a pressure of 100 mm. of mercury is attained in thirty seconds.

Added to this instrument is a safety valve which does not allow the pressure within the Fallopian tubes to exceed 230 mm. of mercury. This safety device is an essential and component part of the instrument.

The single control feature of the mechanism makes for ease and certainty in doing tubal insufflation. From this one point of control the operator can do the test for diagnostic purposes or give a therapeutic insufflation.

The machine consists of the following parts: (1) A tank of compressed gas ( $\text{CO}_2$ ), (2) a syphon meter bottle, (3) a clock mechanism precision kymograph, (4) a reducing valve, (5) two special valves, and (6) a safety valve.

1. The compressed gas ( $\text{CO}_2$ ) is the medium introduced to determine patency.

2. The syphon meter bottle measures the amount of gas which has passed through the cannula. This bottle is so constructed that with each bubble 30 c.c. of carbon dioxide are delivered in thirty seconds.

3. The kymograph is an aneroid recording manometer. Depending on the resistance to the insufflated gas, the pen on the kymograph rises and records the pressure in millimeters of mercury. The chart on the kymograph is graduated along the radius in millimeters of mercury and around the circumference in minutes of time.

4. The reducing valve brings the pressure within the supply tank from 750 pounds pressure to 10 pounds pressure.

5. Two special valves are used to prevent the pressure from rising beyond the outside limit of 15 pounds, and to control the evenness of the flow to the cannula.

6. A safety valve which automatically stops the flow of gas through the instrument after a pressure of 230 mm. of mercury has been reached.

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\*Presented at a meeting of the Obstetrical Society of Philadelphia, January 4, 1940.

Two gauges are visible on the panel of the instrument. The one on the left indicates the amount of carbon dioxide present in the supply tank. The other indicates the number of pounds pressure the gas is being delivered to the cannula.

The single control dial has three positions for use. The "OFF" position, in which no gas is flowing through the system and the kymograph is not recording. The "ON" position, in which the gas flows through the system and the kymograph is in operation. The "TREATMENT" position, at which time the kymograph

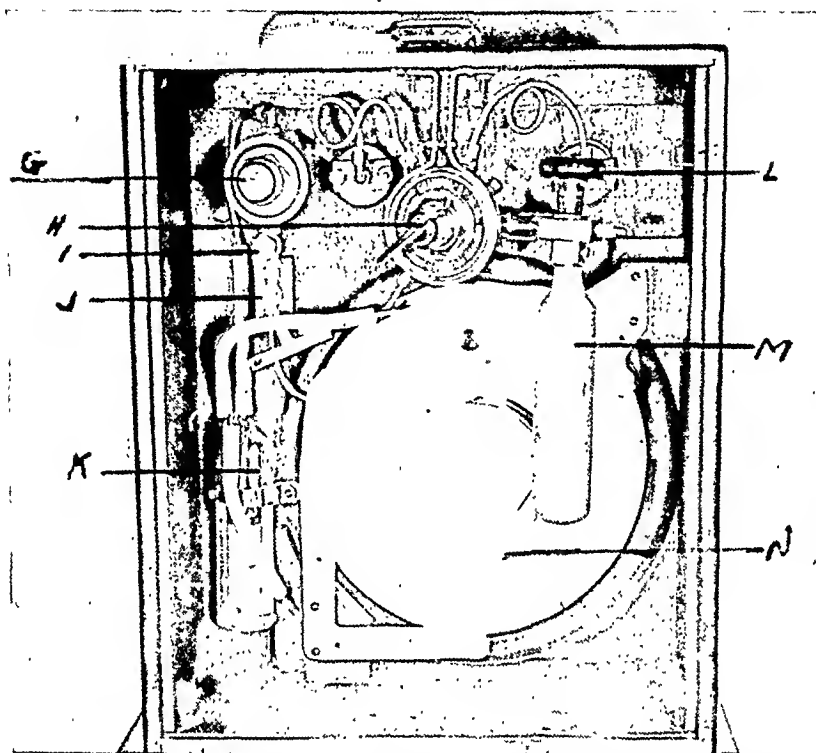


Fig. 1.—Interior view of mechanism. *G*, Safety valve which prevents pressure from exceeding 220 mm. *H*, Regulator to keep pressure in system at 10 pounds level. *I*, Valve to control flow to 60 c.c. per minute and rise of pressure to 100 mm. in thirty seconds. *J*, Rear view of control dial. *K*, Rear view of syphon meter bottle. *L*, Valve to open CO<sub>2</sub> tank. *M*, CO<sub>2</sub> Supply tank. *N*, Rear view of kymograph.

is in operation but no gas is flowing. This "treatment" position is used for therapeutics, since the operator can change the optimum pressure desired with the dial set at "on" and then when the pressure has been reached the dial is set at "treatment." This maintains the pressure within the tubes at a constant level, and we may record the time the treatment has been given.

At the bottom of the panel is a Luer connection into which the cannula tubing is placed.

The procedure then for doing a tubal insufflation with this apparatus is as follows: (1) Open the main supply tank (CO<sub>2</sub>), (2) attach the cannula to the Luer connection, (3) turn the control dial to "on" after the cannula has been inserted into the cervical canal.

Instrument made by W. and G. Scientific Instrument Co., Philadelphia, Pa.

255 SOUTH SEVENTEENTH STREET

# Society Transactions

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## NEW YORK OBSTETRICAL SOCIETY

*MEETING OF JANUARY 9, 1940*

The following papers were presented:

**Sex Hormones in Carcinogenesis.** Dr. Cornelius P. Rhoads (by invitation).

**Carcinoma of the Cervix in a Seven Months Old Infant.** Dr. Edward G. Waters. (For original article, see page 1055.)

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## OBSTETRICAL SOCIETY OF PHILADELPHIA

*MEETING OF JANUARY 4, 1940*

The following papers and case reports were presented:

**Friedman Tests With Ovarian Pregnancy.** Drs. Carl H. Davis and V. Stevens-Young. (For original article, see page 1063.)

**An Automatic Recording Apparatus for Tubal Insufflation.** Dr. A. Herbert Marbach. (For original article, see page 1072.)

**An Experiment in Cancer Control.** Drs. Catherine Macfarlane, Faith S. Fetterman and Margaret C. Sturgis. (For original article, see page 983.)

**Results of Treatment in Carcinoma of the Uterine Cervix.** Dr. Roseoe W. Teahan (by invitation) and Dr. Hoke Wammoek. (For original article, see page 995.)

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## CHICAGO GYNECOLOGICAL SOCIETY

*MEETING OF DECEMBER 15, 1939*

The following papers were presented:

**A Clinical Study of Stilbestrol.** Dr. M. Edward Davis. (For original article, see page 938.)

**Pseudouterus Arcuatus and Functional Malformations of the Uterus.** Dr. Louis Rudolph.

**Angular Pregnancy.** Dr. Ralph E. Campbell and Dr. John L. Parks.

*MEETING OF JANUARY 19, 1940*

The following papers were presented:

**Episodes in the Doctrine of the Three Germ-layers.** Dr. George L. Streeter, Baltimore, Md. (by invitation).

**Hemorrhage in the Late Puerperium.** Dr. Herman A. Strauss. (For original article, see page 1065.)

**Cancer of the Cervix in a Virgin With Intact Hymen.** Dr. A. F. Lash. (For original article, see page 1070.)

# Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

## Selected Abstracts

### Complications of Pregnancy

Solomons, Bethel: Is It Ever Necessary to Kill a Live Baby? Brit. M. J. 1: 1175, 1939.

The author discusses the destruction of the fertilized ovum, both intentional and accidental, at all stages of pregnancy.

Hyperemesis gravidarum is considered an indication for terminating the pregnancy only if in spite of thorough treatment for three to five days the Van den Bergh bilirubin reaction is positive, if there is marked albuminuria, if the pulse rate is increasing and the pulse is getting weaker, or if the patient is becoming jaundiced.

A "renal toxemia" occurring from the twenty-fourth to the twenty-eighth week is considered an indication for hospitalization so that the pregnancy may be carried to the point of viability.

Uncompensated cardiac disease is occasionally an indication for induction during the first three months; after this time treatment of the heart condition is indicated. Tuberculosis and renal disease are best treated on medical lines, also Graves' disease except when the patient is rapidly going downhill after about a month of treatment when termination may be considered.

After the twenty-eighth week the author considers the fetus viable and the occurrence of any of the above conditions may be an indication for induction of labor. However, he considers it unjustifiable to perform craniotomy on the live child, particularly since the advent of the comparatively safe lower segment section. The author reports a series of 122 of these cases, 4 of which resulted in maternal deaths.

The author believes physicians kill live babies more often when inertia is present than in any other condition. He classifies inertia as primary and secondary.

The secondary type, due to some discoverable cause, is dealt with accordingly.

The primary type, without discoverable cause, should be treated conservatively and should be interfered with only when labor has lasted from two to four days, when the temperature and pulse rise, and when the fetus shows signs of distress.

The frequency of resort to cesarean section is deplored as is the abuse of the oxytocies.

The author concludes that the fetus should practically never be destroyed.

FRED L. ADAIR AND JOHN NEWDORP.

Cotte and Magnin: Pregnancy After Myomectomy, Gynéc. et obst. 39: 210, 1939.

The question of pregnancy after myomectomy is discussed by the writers on the basis of their series of 60 cases of myomectomy. Of the 40 women who were capable of childbearing, 11 had one or more children after the operation. They emphasize that in the women who remained sterile after myomectomy associated lesions present during the operation were responsible for the sterility. Thus, among 33 women in whom the tubes and ovaries were normal at the time of the myomectomy, 10 had one or more pregnancies following the operation. On the other hand, of 8 women who had one tube and ovary removed at the time of the myomectomy because of adnexal disease, only one became pregnant; her case is reported in this paper.

In the authors' total series of 40 cases, pregnancy followed 16 times. Of these, 13 went to term and resulted in living children while 3 terminated in miscarriage. These figures are the best argument in favor of conservative operative treatment of uterine myomas.

J. P. GREENHILL.

Naujoks, H.: *Hyperemesis Gravidarum and Ileus in Pregnancy*, Ztschr. f. Geburtsh. und Frauenheilk. 1: 60, 1939.

The treatment of hyperemesis gravidarum is still a serious problem; in some cases the condition becomes worse even in spite of emptying of the uterus. In the author's series at Königsberg, among 82 cases of excessive vomiting there were 12 interruptions of pregnancy and 2 deaths, and among 231 cases in Cologne there were only 5 therapeutic abortions and 1 death. In the latter case chronic ileus was present. The author reports additional cases of true ileus and emphasizes the difficulties in making a correct diagnosis. The mortality in such cases varies between 40 and 60 per cent. Therefore, in every case of severe vomiting during pregnancy, one should not conclude that the patient has hyperemesis gravidarum but must consider every possible cause of vomiting. One should look especially for old laparotomy scars. The author found such scars in 22 per cent of his hyperemesis cases and he considers these suspicious of the presence of adhesions which may be the cause of a beginning ileus. Whenever doubt exists concerning a possible intestinal obstruction, an exploratory laparotomy should be performed without delay.

J. P. GREENHILL.

Dix, Victor W., and Evans, Horace: *Ureteric Catheterization in Pyelitis of Pregnancy*, Lancet 2: 176, 1939.

The authors reviewed a series of 84 cases of pyelitis of pregnancy which were admitted to the London Hospital during the years 1934-1937. All patients were treated with alkalization using potassium citrate dr. 1 at two-hour intervals for eight doses and then at four-hour intervals until the patient became afebrile. Fluids are not forced but should not be less than 2,000 c.c. a day.

In 7 cases additional treatment was necessary. This consisted of ureteral catheterization with continuous drainage for four days and gave excellent results. All of this group have remained free of symptoms subsequent to delivery. In one patient a second catheterization was necessary during the course of pregnancy. Excretion pyelography and examination of the urine have shown no abnormality in 5 cases although 2 have had subsequent pregnancies. In 1 case the follow-up was incomplete. The other case seen at the sixth month of a second pregnancy was symptom free but showed pus and *B. coli* in the urine.

Where pyuria persists post partum the authors suggest the use of mandelic acid to clear up residual infection and prevent dangerous sequelae. They feel that premature induction of labor should rarely, if ever, be necessary.

CARL P. HUBER.

Bussabarger, Cuthbert, and Ivy: *Studies on the Anemia of Pregnancy in Gastrectomized and Normal Dogs*, J. Lab. & Clin. Med. 24: 24, 1938.

In an investigation on the anemias of pregnancy, these authors observed 5 gastrectomized dogs through a total of 15 pregnancies and a control series of 12 normal dogs through 12 pregnancies. The gastrectomized dogs were under observation from 2 to 7 years. The hematologic studies consisted of red blood counts and hemoglobin determinations, and later included hematocrit and blood volume determinations, and in 2 cases mean cell diameters. The results of this experimental series were as follows: Marked to severe anemia developed in the gastrectomized dogs in 11 pregnancies; blood volume determinations made in 8 pregnancies showed a decrease in total circulating hemoglobin of from 20 to 155 Gm. In 2 gastrectomized dogs subjected to extensive enterectomy, the anemia of pregnancy appeared to be less than before this operation. In the control dogs, marked

anemia of pregnancy occurred in 1 case; and in one, anemia of the puerperium was more marked than the anemia of pregnancy. Blood volume determinations in 8 pregnancies showed hydremia in 3 cases.

WILLIAM B. SERBIN.

Moore, Robert A., and Pastore, John B.: Note on Erythroblastic Splenomegaly Occurring During Pregnancy, *Am. J. Med. Sc.* 198: 187, 1939.

The reported case presents several factors which may be significant. During pregnancy the metabolism of iron is increased and the occurrence of anemia is more common than in nonpregnant women. An additional slight disturbance of the erythrogenic tissue might therefore result in conspicuous alterations. There are abundant evidences of infection in the present case: a lobar pneumonia two months before death, latent pulmonary tuberculosis, urinary infection with multiple abscess of the kidney, and a history of repeated attacks of rheumatic fever. The history of a positive Wassermann test is of doubtful significance because of the absence of anatomic changes of syphilis. It is possible that one or more of the infections, combined with pregnancy, induced the alterations of the hematopoietic tissue.

A case of conspicuous extramedullary erythropoiesis with splenomegaly but without significant alteration of the bone marrow is reported. It was associated with lobar pneumonia during pregnancy but there is insufficient evidence to determine the etiology and pathogenesis.

J. THORNWELL WITHERSPOON.

Loehnerberg, Ernst: Hemorrhage From Subserous Varix During First Stage of Labor, *West. J. Surg.* 47: 626, 1939.

Hemorrhages from ruptured varicose veins of the genital organs are rare but serious complications of pregnancy. Varices are commonly found in the external genitalia, and only rarely on the surface of the uterine body. Rupture of internal varicosities is not very unusual, but extremely serious because the resulting hemorrhage is sudden, severe, unanticipated, and often so rapid that medical aid comes too late.

One personally observed case of this sort is reported by the writer. Patient was first seen with a spontaneous abortion attributed to a fixed retroversion. She conceived again three years later. Ten days before expected confinement the patient experienced mild uterine contractions accompanied by occasional very severe pain in lower abdomen. Contractions stopped. Two days later patient was found to be extremely anemic. Pulse fast and thready. Abdomen greatly distended and tender. Cervix dilated to 3 cm., head movable above inlet. Diagnosis of severe internal hemorrhage was made, premature detachment of normally inserted placenta being suspected. During preparation for section patient became progressively worse, finally pulseless. Laparotomy revealed an enormous mass of free blood in abdomen. An asphyxiated child weighing 3,780 Gm. was delivered which could not be resuscitated. Inspection showed a ruptured varix on the posterior surface of the uterus, 4 cm. above cervical level. To save time uterus was amputated. Patient recovered after a stormy convalescence.

Of 13 cases found in literature, 6 were saved. In only one instance a correct preoperative diagnosis had been made.

HUGO EHRENFEST.

Brown, Clark E., and Eder, Lawrence F.: Acute Puerperal Hypophyseal Necrosis With Report of a Fatal Case, *Am. J. M. Sc.* 198: 166, 1939.

An acute thrombosis and necrosis of the anterior pituitary, terminating fatally during the puerperium, occurred in a woman aged 46 years. An endocrine deficiency resulted therefrom. Acute pituitary necrosis may be a more common puerperal complication than is usually recognized. Should the puerperal course of a patient progress unfavorably without obvious cause, blood sugar studies, active glucose therapy, and anterior pituitary extracts should be in order.

J. THORNWELL WITHERSPOON.



Portes and Varangot: Indications for Oophorectomy During Pregnancy, *Gynéc. et obst.* 39: 98, 1939.

It is not necessary to remove every ovarian cyst diagnosed during pregnancy. If an operation must be performed it should be carried out as late as possible. Ovarian cysts should not be removed unless they produce mechanical effects or if they are infected. Complications include torsion, hemorrhage and suppuration. If an operation is performed, the corpus luteum should not be removed. This is readily accomplished if the corpus luteum is in the healthy ovary, but even if it is in the ovary which contains the cyst, the latter may usually be shelled out leaving the yellow body in place. If it is impossible to save the corpus luteum the patient should receive massive injections of progesterone every day for a long time, instead of counting on the secretory activity of the placenta.

J. P. GREENHILL.

Brindeau, A.: Aseptic Necrobiosis of Fibromyomas in Pregnant Women, *Rev. franc. de gynéc. e d'obst.* 34: 193, 1939.

Among 59 women operated upon for aseptic necrobiosis of fibroids during pregnancy, 5 died. In 18 cases Brindeau performed a hysterectomy and in this group 2 women died. In 41 cases he performed a myomectomy and of these 3 died. In 88 per cent of the cases where myomectomy was performed the pregnancy continued uninterruptedly. It is Brindeau's belief that aseptic necrosis of fibroids is a very frequent occurrence during pregnancy, which seldom produces disturbances. When complications occur they are due to acute necrosis, a rapid hypertrophy of the fibroid, torsion of the pedicle, infection or marked change in the general condition.

Treatment consists of the following: When the necrosis is uncomplicated, conservatism should be practiced. Surgical intervention is necessary only when complications arise. Myomectomy is the treatment of choice. During labor if the tumor does not produce dystocia, delivery should be permitted to take place through the vagina. If, however, the tumor blocks the exit of the child, the pregnancy should be permitted to go to term or the onset of labor. Then a low cesarean section should be performed followed by myomectomy or hysterectomy. During the puerperium aseptic necrosis is usually innocuous. If infection sets in, immediate hysterectomy must be carried out.

J. P. GREENHILL.

Johnson, W. O.: Polypous Cervical and Vaginal Hyperplasias in Association With Pregnancy, *South. M. J.* 32: 577, 1939.

Eight cases are presented of hyperplasia of the vagina and cervical mucous membrane in association with pregnancy, which simulated carcinoma, but which disappeared after the termination of pregnancy. Possible causes of such hyperplasias are abnormal hormonal stimulation of the vaginal mucous membrane in association with pregnancy or deficiency of vitamins A and D. These conditions are not dependent on race and do not necessarily recur. Usual methods of cleanliness are sufficient to relieve symptoms during pregnancy. After delivery the lesions disappear and leave no scarring of the vagina. Radium therapy is not indicated, and termination of pregnancy is unnecessary. Post-partum infections have not occurred in this series, and the hyperplasias have all disappeared within two months after delivery.

J. P. GREENHILL.

Hansen, R.: Uterine Carcinoma and Pregnancy, *Ztschr. f. Geburtsh. und Frauenheilk.* 1: 49, 1939.

Carcinoma of the uterus which is associated with pregnancy almost exclusively involves the cervix. During the past three years Hansen has observed 5 cases of cervical cancer in a series of 3,500 pregnant women. The symptoms of cancer during gestation are those of the nonpregnant state, the most frequent being bleeding. There is no agreement as to the effect of pregnancy on cancer for some

## ANALYSIS OF RESULTS

Relatively small amounts (10 to 30 mg.) of testosterone propionate are required to lessen the bleeding materially, i.e., reduce the flow to a dribble. A somewhat larger amount is required to stop the bleeding completely. The dosage schedule employed stands in marked contrast to that of others<sup>11</sup> who recommended dosages of two hundred to two thousand mg. However, while this paper was being prepared, Beclere<sup>12</sup> reported that very moderate doses were needed (25 to 50 mg.) to control excessive bleeding. On the basis of the calculations of Kenyon<sup>13</sup> it is felt that single doses of 5 to 25 mg. are within physiologic limits. A phenomenon that may explain the large dosages used by the workers quoted above is, that quite frequently, following a slight immediate reduction in flow, there may occur a more or less marked exacerbation of flow which may last from three to twelve hours or more. Injections of testosterone propionate should not be given at this point, for the increased flow may be extended over a still longer period of time. (In one case, not reported here, it lasted five days.) This transient increase of flow is almost pathognomonic of a subsequent sharp decrease and rapid cessation of flow. This phenomenon is noted whether testosterone propionate is administered intramuscularly, subcutaneously, or orally.<sup>1</sup> It has also been noted with pregnancy urine extracts and with progesterone.<sup>14</sup> It is because of this temporary increase that injections are given every two to four days instead of daily.

Second, the route of administration seems to play an important role in determining the total dosage required to control the bleeding. The subcutaneous route provides for a more prolonged and thus for a more effective per-dose action.<sup>15</sup> However, in actively bleeding cases, the first injection was given entirely intramuscularly for a rapid initial action, or else it was divided between the intramuscular and subcutaneous routes to sustain and prolong the initial reaction over a longer period of time. Case 1 revealed that under essentially similar conditions the dosage required by the subcutaneous route was one-half that required by the intramuscular route. This patient was on one occasion given 100 mg. of testosterone propionate in divided doses in the ten days before her period. Endometrial biopsy taken at the start of injections and on the fourth day of the succeeding period revealed endometrial hyperplasia both times. Even though a considerable reduction in flow had resulted, the endometrium had apparently not been affected at all. This finding, combined with the observation that three patients were found to be bleeding profusely from a different type of endometrium on separate occasions, serves to substantiate further the contention that it is to the myometrium, not the endometrium, that we must look for the factors controlling the amount and duration of uterine bleeding.

## SUMMARY AND CONCLUSIONS

On the basis of certain physiologic properties of testosterone, a therapeutic rationale for its use in the treatment of metromenorrhagia was developed along physiodynamic lines. This has been founded in main on the action of testosterone on the myometrium, since the myometrial elements play such an essential role in the control of the amount of uterine bleeding.

The action of testosterone is, first of all, inhibition of rhythmic intermittent contractility, thus lessening the volume flow of blood to the uterus. Second, by its direct effect on the myometrial elements, the volume flow of blood in the myometrium is reduced. The net result is a diminution in the flow of blood to the endometrium with a consequent reduction in the amount of uterine bleeding.

The immediate treatment of metromenorrhagia with testosterone propionate proved to be highly successful.

the first half of pregnancy, and the blood pressure of women suffering from hypertension may fall within normal limits during this period of gestation. The water balance is disturbed during the second half of a normal pregnancy. This disturbance precedes hypertension, which itself precedes albuminuria. This sequence of events may be caused by hepatic malfunction and may be the result of abnormal proteins circulating in the blood. It is suggested that a high blood urea content may be considered an index of hepatic malfunction.

There are two main groups of women in whom it is possible to predicate before marriage that they are likely to suffer from pre-eclampsia or eclampsia: (1) those with glomerulonephritis resulting from the exanthems and tonsillitis; (2) those with a blood urea content exceeding 40 mg. per cent and who are unable to concentrate this substance in the urine. These women will, apart from suitable treatment, manifest toxemic symptoms in each successive pregnancy.

It is suggested that the hepatic malfunction resulting in the presence of abnormal proteins in the blood plasma is caused by a meat diet associated with a disturbance of the calcium metabolism and an insufficient intake of the vitamin B complex.

The remarkable association of heredity with the hypertension of pregnancy not only makes it reasonable to place this condition in the same category as hypertension occurring in the nonpregnant state but warrants the assumption that hypertension of pregnancy is merely an exacerbation of the insidious process which ultimately results in death.

There is no evidence of a causal relation between pregnancy and chronic nephritis. A woman with chronic glomerulonephritis may pass through pregnancy without further damaging her kidneys providing the condition has not progressed sufficiently far to embarrass her general health and certain tests for renal efficiency prove satisfactory.

Death of the fetus in utero is to be attributed to dietetic deficiencies. If it is true that hypertension of pregnancy presents an exaggerated picture of the march of hypertension in man, then it is obvious that the obstetrician has the unique opportunity of contributing to knowledge of the early stages of chronic glomerulonephritis and of the causation of some forms of arteriosclerosis and renal failure, for he sees the patient ten years before she consults the physician with symptoms attributable to the conditions. If there is no causal relation between pregnancy and chronic nephritis the last need for postulating a pregnancy toxin has disappeared.

J. P. GREENHILL.

Page, E. W., and Cox, A. J.: Renal Changes Following Toxemias of Late Pregnancy, *West. J. Surg.* 46: 463, 1938.

Clinical follow-up studies on 96 cases of eclampsia substantiate the findings in the collected literature that recurring toxemias, hypertension and albuminuria are frequent sequelae of the toxemias of later pregnancy. The nature of the residual renal lesion following eclamptogenic toxemias was investigated by the examination of kidney tissue from 26 selected autopsies. Thickened glomerular capillary membranes were demonstrated in the kidneys of eight patients dying during toxemias of late pregnancy. Seven women who were known to have had previous toxemias of varying severity, and who died of miscellaneous causes, uniformly showed similar changes in the glomerular capillary membrane. This glomerular lesion is not specific for eclampsia since slight degrees of similar changes were found in five of 11 women who had had normal pregnancies and who died from various causes unrelated to eclampsia.

J. P. GREENHILL.

believe that carcinoma grows more rapidly during gestation, whereas others maintain the reverse. There is, however, unity of opinion concerning the harmful effect of carcinoma on the course of pregnancy. In 30 per cent of the cases there is a spontaneous abortion. During labor there are two dangers, namely laceration with resultant hemorrhage and inability of the cervix to dilate. In the puerperium there always occurs extension of the carcinoma unless the uterus has been removed. Likewise the bacteria from the carcinomatous areas enter the uterus and frequently produce puerperal infection.

The treatment of carcinoma of the cervix during pregnancy is as follows:

1. At the end of pregnancy and during labor in the presence of a living child in an operable case, a Wertheim operation should be performed without opening the uterus and this should be followed by roentgen-ray therapy. In inoperable cases, a Porro operation should be performed on the unopened uterus and followed up by radium and roentgen-ray therapy. Spontaneous labor should never be awaited in any case of cancer of the cervix.

2. During pregnancy when the child is not viable, in operable cases, a Wertheim operation should be performed with postoperative radiation treatment. In inoperable cases, the uterus should be amputated and the patient receive postoperative radiation therapy.

J. P. GREENHILL.

Newell, Q. U., and Scrivener, W. C.: *Pregnancy and Cervix Cancer*, South. M. J. 32: 818, 1939.

The occurrence of cancer of the cervix with pregnancy is very infrequent, probably because the age group for malignancy and for childbearing do not coincide. In 27,952 obstetric admissions there were only 7 cases of carcinoma of the cervix, an incidence of 1 in 4,000. Summaries of 8 cases are presented.

Diagnosis is frequently delayed, either because vaginal bleeding is ignored by the patient, or the physician interprets the symptom as a sign of threatened abortion and neglects to make an examination. Association of cervical cancer and pregnancy is more frequent in multiparas, suggesting that the trauma of parturition may be an etiologic factor. Pregnancy probably accelerates the growth of malignancy. Bleeding during gestation should be investigated and cervical biopsy performed when indicated.

Treatment has not been standardized. Treatment of the malignancy should take precedence over consideration for the pregnancy. The authors employ the League of Nations clinical classification of pelvic cancer, and they apply therapy according to four arbitrarily designated periods of pregnancy. Up to four and one-half months, total hysterectomy followed by x-ray therapy is advocated for Groups 1 and 2. For Groups 3 and 4, cervical application of radium should precede supravaginal hysterectomy and radiation.

For a gestation of four and one-half to seven months in lesions in Groups 1 and 2 the radical operation and irradiation is preferable. As an alternate procedure, 4,000 mg. hours of radium applied to the cervix with screening to protect the fetus. Advanced lesions should be treated by high supravaginal hysterectomy and tandem insertion of radium in addition to x-ray therapy. Beyond seven months, screened radium implantation in the cervix with Porro cesarean section at term and subsequent irradiation. At or near term, the same procedure is advocated, except that radiation is prescribed after operation.

Radiation is followed by a satisfactory response, and it is relatively safe for the patient and the baby.

Vaginal delivery in these patients is contraindicated.

ARNOLD GOLDBERGER.

Theobald, G. W.: *Relation of Pregnancy to Hypertension and Chronic Nephritis*, J. Obst. & Gynaec. Brit. Emp. 43: 1037, 1936.

Women who normally suffer from albuminuria tend to pass protein-free urine during the first six months of pregnancy. The blood pressure normally falls during

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\*January, pp. 1-178; February, pp. 179-364; March, pp. 365-548; April, pp. 549-732; May, pp. 733-918; June, pp. 919-1102.

The average minimal dosage required to lessen the bleeding materially varied from 10 to 30 mg. The total dosage necessary to stop the flow completely ranged from 10 to 120 mg., with an average of 40 to 60 mg. Two to four injections at intervals of two to four days were usually found sufficient. Injections should not be repeated during the transient exacerbation of bleeding which frequently occurs.

The subcutaneous route seems to provide for a more effective per-dose action, hence requires a smaller total dosage to achieve a therapeutic result. Where the flow was very profuse and free, the initial injection was given intramuscularly for a rapid initial action.

The only possible sign of defeminization ever observed was the loss of libido in two patients.

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**Osborn, G. R., and Dawson, J. C. C.**: Air Embolism, Lancet 2: 770, 1938.

Three instances of death following air embolism are reported, two in women following full-term delivery. In one case, death occurred three hours after cesarean section performed for a contracted pelvis and a large uterine fibroid. Temporary collapse followed incision of the uterine wall; but cyanosis persisted and obvious air hunger developed postoperatively. The second case followed natural delivery and apparently occurred following expression of blood clots from the uterus one-half hour post partum. Death ensued in one and one-half hours. Autopsy revealed a partial inversion of the uterus.

The characteristic symptoms of air embolism are described as sudden onset; disappearance of the pulse; deep respirations with air hunger; restlessness with chest discomfort; pallor if the case is fatal in one to two minutes and cyanosis if death is delayed.

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# INHIBITION OF LACTATION DURING THE PUERPERIUM BY TESTOSTERONE PROPIONATE

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EXPERIMENTAL inhibition of lactation in mice has been accomplished with crystalline estrone by de Jongh<sup>1</sup> and Robson.<sup>2</sup> Enzmann and Pincus<sup>3</sup> inhibited milk secretion in lactating mice, and de Jongh<sup>4</sup> produced the same results in normal and ovariectomized lactating mice. Selye, Collip and Thompson<sup>5</sup> observed the inhibitory effect on lactation in rats after injection of anterior pituitary-like and pig pituitary extract. Cannon<sup>6</sup> confirmed these findings. Robson<sup>7</sup> demonstrated in mice, and Folley and Kon<sup>8</sup> in rats that testosterone propionate inhibited lactation, while androsterone and progesterone were ineffective. Anselmino and Hoffmann<sup>9</sup> showed that progesterone does not exert an inhibitory action on the secretion of milk.

R. Kurzrok and O'Connell demonstrated recently that it is possible to inhibit lactation in women during the puerperium by the administration of male sex hormone in the form of testosterone propionate.

We are reporting a series of 56 patients treated with testosterone propionate in an attempt to inhibit lactation post partum. In order to determine the optimum dosage, the amount of sex hormone was varied, and in order to determine the most advantageous time of administration the injections were given at different stages after delivery. Most of these patients had normal deliveries; some were delivered by forceps, either elective or indicated, and several by cesarean section. These patients had no treatment to inhibit lactation other than testosterone propionate. Saline cathartics were not given and fluids were not restricted. Six patients had adhesive strapping and constrictive sheet binders because of pain and engorgement in the breasts. Most of the patients who had already begun to lactate complained of pains in the breasts, engorgement, and not infrequently showed an elevation of temperature prior to treatment. Indications for the avoidance of suckling were: (1) Cracked nipples, (2) premature infants, (3) stillborn infants, (4) refusal of mother to nurse child, (5) constitutional disease in mother, such as cardiac disease, pyelitis, etc.

Injections were given intramuscularly into the gluteal region. The male sex hormone had no apparent effect upon the amount or continuance of the lochia, involution of the uterus taking place at the normal rate. There were no unpleasant after effects, nor were any local infections or reactions noted. There were no painful contractions of the uterus following the injections, nor was there any effect on afterpains in those patients, particularly multiparas, who did complain of the usual cramps. Results were equally as good in multiparous and primiparous women. Onset of the first menstrual period was not delayed in those patients observed postpartum, nor did the bleeding differ in any way from that usually seen.

We have divided our cases into the following groups:

*Group 1.*—Two patients were treated by administration of 100 mg. of testosterone propionate on the day of delivery, in divided doses of 25 to 50 mg. Lactation was completely inhibited.

*Group 2.*—In 29 patients treatment was begun three days after delivery, 125 mg. of male sex hormone being given, usually in doses of 50, 50 and 25 mg. at twelve-hour intervals. In several cases, 25 mg. was administered every four hours. Ten patients complained of some engorgement and pain in the breasts for twelve to thirty-six hours, and binders or adhesive strappings were used in 8 cases. Ice bags were applied in 2 cases. Lactation occurred in these patients, but lasted only three to six days, and was never considerable in amount. The remaining 19 patients had



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excellent results, lactation either not occurring or being present to a diminished extent for a few days without pain and congestion of the breasts.

*Group 3.*—In 11 cases treatment was begun 4 to 5 days postpartum. Five patients had good results, one patient requiring an additional 25 mg., making a total dosage of 150 mg. One patient obtained no relief from 100 mg. given in 2 injections of 50 mg. each, the breasts being hard and painful for the next twenty-four hours; at this time, another 100 mg. was administered, with marked relief within twelve hours. Four patients given an individual injection of 100 mg. showed little or no benefit, even when an additional 25 mg. was given.

*Group 4.*—In 8 patients, treatment was started from 6 to 9 days after delivery. One failure occurred, this patient receiving an individual dose of 100 mg. The other 7 patients responded favorably within twenty-four hours after the last dose, 125 to 150 mg. being administered in divided doses. One patient developed an elevated temperature of 105° shortly after the first injection; however, this was due to a concomitant pyelitis.

An interesting problem occurred in a multipara who returned to the hospital two weeks post partum because of bleeding. A diagnosis of retained secundines was made. The temperature of the patient had varied between 100° and 104° F., and nursing had been continued until admission to the hospital. The breasts were engorged and tender; 100 mg. of testosterone propionate was given, followed by 20 mg. twelve hours later. Within thirty hours, lactation had almost entirely ceased, the breasts were soft and not painful.

Another patient, a multipara, was delivered spontaneously after a short labor. During a previous pregnancy she had developed a mastitis, which subsided after several days. Four weeks following the recent delivery of a child she developed a fissure of the left nipple. Nursing produced frank bleeding, and breast feeding was discontinued; an ice cap was applied to the breast as well as an adhesive binder for twenty-four hours; 100 mg. of testosterone propionate was administered followed by 50 mg. at twelve-hour intervals until 250 mg. had been given. Within forty-eight hours after the final dose, the breast no longer lactated. Unfortunately, softening and fluctuation took place, and a breast abscess had to be incised. At no time after treatment did lactation occur. Secretion had ceased almost entirely within twelve hours after the injections.

#### DISCUSSION

1. At the present time we are unable to determine exactly the optimum time to administer the testosterone propionate in order to obtain optimum results.

2. Good results were uniformly obtained when the dose ranged between 125 and 150 mg. This dosage was apparently higher than that found necessary by R. Kurzrok and O'Connell.

3. Lactation, engorgement, and pains in the breasts did not recur after treatment was stopped.

4. Apparently better results were obtained when the total amount of medication was given in divided doses of 25 to 50 mg.

5. Individual doses of 100 and 125 mg. were generally ineffective regardless of the time of administration.

6. Fifty-six patients, post partum, were treated with testosterone propionate to inhibit lactation. Forty-nine patients responded favorably to this therapy. There were 7 failures in this series.

Since it is definitely possible to inhibit lactation by the use of testosterone propionate either before or after actual lactation has set in, we believe the mode of action of the drug is by inhibition of the pituitary, as demonstrated experimentally in animals. The fact that lactation can be prevented before its onset is evidence that the inhibitory effect is not on the end organ, namely, the breast tissue, but indirect, through the pituitary.

We wish to thank Drs. Irwin Sehwenk and Max Gilbert of the Sehering Corporation for their very helpful cooperation and for the generous amounts of material which they supplied.



The inhibition of lactation in the human being with testosterone propionate was encouraged by R. Kurzrok. Kurzrok's theoretical explanation for the action of this preparation is that testosterone suddenly inhibits the action of prolactin, the activator of the mammary gland, at the time of lactation. Robson<sup>7</sup> found that injections of testosterone propionate in oil, 0.1 mg. daily for twenty days, would rapidly bring lactation to an end in mice.

Kurzrok and O'Connell<sup>8</sup> have used testosterone propionate for the inhibition of lactation in doses ranging from 50 to 150 mg. They found success in 19 out of their 21 cases.

At the Brooklyn Women's Hospital from Dec. 1, 1938 to the present time, 50 patients in early lactation during the puerperium were treated with testosterone propionate (oreton). Total doses varying from 25 mg. to 125 mg. were given in divided doses every twelve hours, intramuscularly. No other measures such as breast binders (the latter were used only for support in cases of pendulous breasts), restriction of fluids, ice bags, or magnesium sulphate were used.

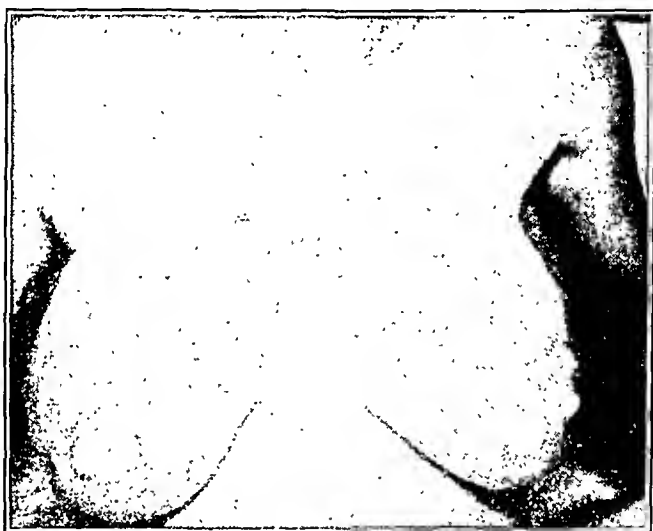


Fig. 1.—Infrared photograph. Note engorgement of breasts before treatment.

The ages of the 50 parturient women were between 20 and 38; 20 were primiparas, 30 multiparas. Thirty-two women delivered spontaneously, 12 with forceps, cesarean section 3, breech extraction 2, embryotomy 1. Reasons for delactation were as follows: Stillbirths 11, inverted nipples 9, section 3, sick infants 6, cracked and sore nipples 5, previous breast abscesses 2, cardiac 1, toxemia 4, bleeding nipples 1, unknown 8. Fourteen patients were treated with 75 mg. divided doses of 3 injections of oreton, 2 with 125 mg. in 5 divided doses, 33 with 30 mg. in 3 divided doses and one with 3 divided doses of 10 mg. each and subsequently one 50 mg. dose. Treatment was started on 4 patients on the second day post partum, 38 on the third day, 4 on the fourth day, 2 on the fifth day, 1 on the seventh day, and 1 on the twentieth day.

Forty-seven out of the 50 cases were definitely successful (94.0 per cent). In these cases, pain in the breasts due to congestion was the first symptom to disappear. On the average, this symptom disappeared eight to twelve hours after the total dose was administered. In all of the successful cases, cessation of lactation and complete involution of the breasts were present as early as the second day following total dosage.

The three unsuccessful cases were as follows:

CASE 1.—Mrs. B. W., aged 24 years, para i, gravida i, low forceps delivery, post-partum course negative, 125 mg. in 5 doses given, starting on the third day post

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## THE USE OF TESTOSTERONE PROPIONATE IN THE INHIBITION OF LACTATION DURING THE PUERPERIUM\*

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THE clinical observations during the lactating period in the puerperal woman and the problem of the inhibition of milk secretion have stimulated this report. In striving for a simpler and newer method of treatment for this uncomfortable condition, the use of testosterone propionate (oreton)† was employed and its results in a series of 50 cases are herewith presented.

The ever-increasing research in endocrinology has been apparent in offering a solution to the close interrelationship between the mammary glands during pregnancy and the puerperium and other hormones. As is well known, the human breast is prepared for lactation by being under the influence of the hormones of the ovary. Estrin has been demonstrated to be one of the factors which controls the growth and activity of the mammary gland.<sup>1</sup> The breast develops under the influence of the follicular hormone, while the corpus luteum hormone is responsible for the construction of alveolar tissues.<sup>2</sup> The work of Corner in 1930<sup>3</sup> suggests that the function of the ovarian hormones is primarily dependent upon the anterior hypophysis. It has also been shown that a specific lactation hormone, termed prolactin by Riddle, is formed in the anterior lobe of the pituitary gland, which is assumed to be the stimulus for milk secretion and has no direct influence on the development of the mammary glands.

Many conditions are encountered in the puerperal woman and child, in which nursing is not advised in some instances, in others it is impossible. Among the latter may be mentioned cardiac conditions, toxemias of pregnancy, cesarean section, stillbirths, miscarriages and missed abortions, unwed mothers, monstrosities, cracked, eroded, and retracted nipples, mastitis, tuberculosis, diabetes and economic reasons.

It has been shown that estrogenic substances have a depressing action on the hypophysis and that the secretion of milk which depends upon the anterior pituitary hormone, prolactin, undergoes the same inhibition. This has led to the use of folliculin in large doses to bring about a reduction in the flow of milk. The results of this treatment have not been very encouraging. Ramos and Colombo,<sup>4</sup> Lindemann,<sup>5</sup> Hoffmann,<sup>2</sup> and Adrian<sup>6</sup> used injections of folliculin in doses ranging from 25,000 to 260,000 rat units daily with variable success. The results with estrogenic substances in the inhibition of milk secretion, although fair, caused considerable afterpains and increased the blood flow in those patients upon whom it was administered.

\*Read at a meeting of the Clinical Society of the Brooklyn Women's Hospital, March 16, 1939.

†Grateful acknowledgment is offered to Schering Corp., Bloomfield, N. J., for their generous supply of oreton for clinical use.



4. Smaller doses of testosterone propionate (three 10 mg. doses) can be used, and have been shown to be quite as effective as larger doses. This is encouraging, inasmuch as this form of treatment is within the economic means of the ordinary patient.

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## ADENOACANTHOMA OF THE UTERUS

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CARCINOMA in general tends to reproduce, in a more or less disorderly fashion, the epithelium from which it arises. Therefore, cancer starting in the uterine cavity is usually composed of a cylindrical type of cell and tries to mimic the surface columnar epithelium and the glandular structures of the endometrium. These tumors are then frequently classified as adenoma malignum, adenocarcinoma, papillary adenocarcinoma, and alveolar or diffuse carcinoma. Occasionally, carcinoma of the body of the uterus is composed of cylindrical and squamous cells and in rare cases only squamous cells. Murphy,<sup>1</sup> in his report of 197 cases of fundal carcinoma admitted to the State Institute for the Study of Malignant Diseases at Buffalo, found but two cases of adenoacanthoma, while Lindsay<sup>2</sup> noted 3 instances in a series of 70 cases of carcinoma of the body of the uterus. Healy and Cutler<sup>3</sup> found 3 adenoacanthomas among 100 cases of carcinoma of the body of the uterus.

Adenoacanthoma, sometimes called adenosquamous carcinoma, is composed of groups of adenocarcinoma and areas of squamous epithelium. Usually the squamous epithelium is a benign accompaniment of the malignant cylindrical cell carcinoma, but it may sometimes undergo malignant change. Novak and Yui<sup>4</sup> believe that the squamous epithelium probably arises from undifferentiated cells beneath the cylindrical epithelium which under appropriate stimulation may develop into squamous epithelium. Occasionally the squamous cells may predominate, but most frequently it is the adenocarcinoma which forms the largest part of the neoplasm. In sections of these tumors one can frequently see how the squamous change occurs from the cylindrical cell thus indicating the primary character of the tumor. Sometimes, the squamous cells may be so few in number that they may be overlooked unless a careful search for them is made.

It is important to differentiate this type of tumor from the others because of its different behavior. Adenoacanthomas of the body of the uterus act similarly to adenocarcinoma of the body but their metastases are more frequent and extensive. The prognosis in these cases, according to Meigs,<sup>5</sup> lies midway between cancer of the cervix and cancer of the body. It responds quite poorly to radium. Healy and Cutler<sup>3</sup> reported three cases of adenoacanthoma which were treated with radium. Of these, one patient died in eleven months, one in 18 months, and the third in three years. According to Ferguson,<sup>6</sup> no reported case has been found where there was complete disappearance of the adenoacanthoma following the application of radium. Meigs<sup>5</sup> states that total hysterectomy, with the removal of both tubes, both ovaries and the cervix, is the proper treatment for this disease. Radium should be used as a palliative measure, as for example, in extensive cases when extirpation is impossible.

partum. Pain disappeared after twenty-four hours. Ninety-six hours after administration breasts only slightly improved, were caked and lumpy and there was no involution present.

CASE 2.—Mrs. P. G., aged 30 years, para ii, gravida ii, spontaneous delivery, post partum negative, inverted nipples, given 75 mg. in 3 doses, third day post partum. Ninety-six hours after administration no improvement, no involution, breasts were still full, hard, and congested.

CASE 3.—Mrs. L. L., aged 20 years, para i, gravida i, low forceps delivery, history of bleeding nipples daily in fourth and fifth months of pregnancy; salpingo-oophorectomy two weeks prior to delivery; given 80 mg. in 4 doses with no results; breasts were still full, congested and continually leaking.

A questionnaire was resorted to in an attempt to follow up the effect of the treatment. Thirty replies were received, the results being the following: (1) Milk did not return to the breasts in any of the 30 cases. (2) Twenty-seven women had no ill effects; 3 had slight pain in the breasts. (3) Twenty-four women men-

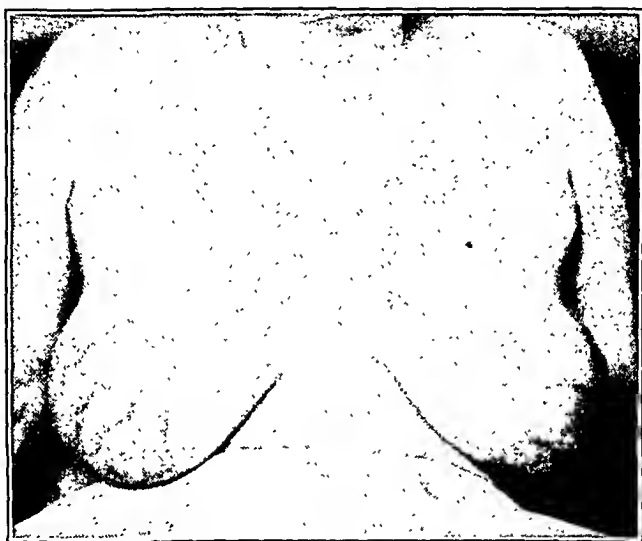


Fig. 2.—Infrared photograph. Note diminished engorgement of breasts after injection with testosterone propionate, 30 mg.

struated promptly approximately six weeks following delivery. In 6 the menstrual flow had not as yet returned. (4) Out of 25 women, whose periods returned, the flow was more profuse than usual in 18, less than usual in 5, usual amount in 2. (5) None of the 30 women noticed any lumps in their breasts up to six weeks following delivery.

#### SUMMARY AND CONCLUSIONS

1. Fifty parturient women were treated with testosterone propionate (oreton) for inhibition of lactation. Two cases were observed as control patients. Successful cessation of lactation with alleviation of all symptoms was obtained in 47 or 94.0 per cent of the cases. The three unsuccessful cases are described.

2. The advantages of the use of testosterone propionate in inhibiting lactation in women during the puerperium are: Its simple administration, its good results, its alleviation of all symptoms in a great percentage of the cases, and the abandoning of other measures such as tight binders, ice bags, restriction of fluids, or magnesium sulphate with its use.

3. Afterpains were not exhibited after the injection of this hormone; likewise was there no evidence of excessive or diminished post-partum bleeding.

*Microscopic Findings.*—The tumor of the uterus was composed of numerous acini some of which were small and others large. These were lined by single or multiple layers of cells which were columnar in type and hyperchromatic. Occasional mitotic figures were present. Some of the larger acini contained within them an amorphous, pink-staining substance within which fragments of nuclear material were present. Here and there groups of squamous cells were noted. In one area the surface of the uterine cavity was lined by a thick layer of large squamous cells (Fig. 1). In other areas of the tumor groups of squamous cells intimately associated with the tumor acini were present (Fig. 2). Here one could see how the columnar cells gradually merged into the squamous type of cell. Large areas of necrosis were present in which broken-down tumor cells were noted. The tubes showed some thickening of their villi but no tumor was noted within the lumen or involving the musculature. On the serosal surface, however, a few small groups of squamous cells were present. The right ovary was infiltrated with numerous tumor acini composed of hyperchromatic, columnar cells, showing occasional mitotic figures (Fig. 3). Large areas of necrosis were present. Areas of squamous cells were also noted. Some of these showed



Fig. 1.

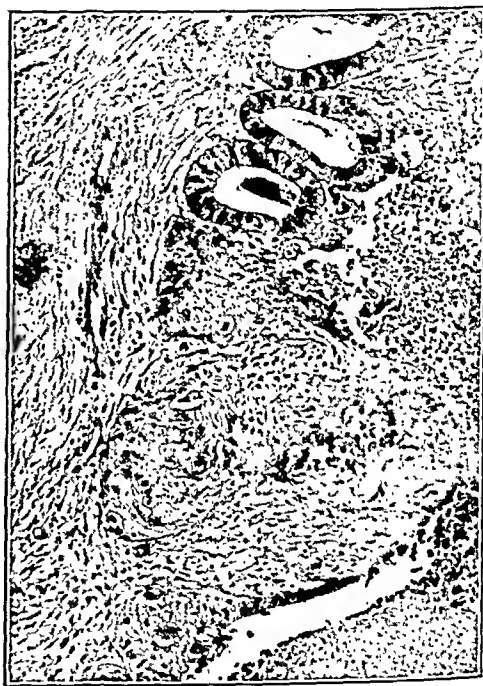


Fig. 2.

Fig. 1.—Section from epithelium lining the uterine cavity, showing thick well-differentiated squamous cells.

Fig. 2.—Tumor of uterus, showing cylindrical cell carcinoma in close association with the squamous cells.

keratinization and an occasional suggestive "pearl" could be seen. Groups of columnar and squamous cells were present and the intimate association between these two different types of cells could be observed (Fig. 4). The stroma of the tumor was composed of a loose type of connective tissue. The left ovary was normal.

*Autopsy Findings.*—The body was that of a well-developed and well-nourished, white female, about 40 years of age, with a body length of 166 cm. and a body weight of 160 pounds. No rigor mortis was present. There was a diffuse lividity in the dependent portions of the body. A decubitus ulcer was present in the sacral region which was not deep and measured 13 cm. in diameter. A linear surgical mid-

## REPORT OF CASE

P. H., a white woman, 42 years of age, was admitted to the hospital Oct. 19, 1938, with the history of acute pain in the right side of the abdomen, accompanied by nausea and vomiting. For the past eight months she had similar attacks of pain in the lower abdomen associated with the above symptoms. Since this time she had anorexia and had lost some weight. Her bowel movements had been irregular. No bloody diarrhea was noted. For the past five months she had a purulent vaginal discharge. For three months previous to admission she had symptoms of urinary frequency and nocturia. The patient had never been pregnant. Her periods had always been irregular and usually lasted five days. For the last six months she suffered with menorrhagia and the last two months she developed metrorrhagia. Thirteen years before admission she bled considerably and was treated by curettage. This ameliorated her condition at that time.

Physical examination revealed a middle-aged woman who appeared very anemic. The pulse was 110, temperature 101.6° F., respiration 20, and the blood pressure 134/94. The skin was cold and clammy. The head revealed no abnormalities. The pupils reacted to light and accommodation. No neck glands were palpable. The breasts were normal. The heart was not enlarged and the sounds were of good quality. No murmurs were heard. The chest expanded equally on both sides and the breath sounds were clear. The abdomen was obese and there was slight generalized rigidity. Abdominal tenderness was generalized but was most marked in the right lower quadrant. Large masses were palpable in both lower quadrants. Vaginal examination revealed a soft, dilated cervix. A fungating mass was noted in the cervical canal. A biopsy taken from this mass revealed adenocarcinoma. The blood picture on Oct. 19, 1938, showed a hemoglobin of 100 per cent, red blood count 5,100,000, white blood count 10,900, polymorphonuclear neutrophils 84 per cent, and lymphocytes 16 per cent. The sedimentation rate was twenty minutes. On Dec. 18, 1938, the red blood cells were 4,400,000 and the white blood cells 4,000. Urine examination on Oct. 19, 1938, was negative. On Oct. 22, 1938, examination showed many red blood cells and epithelial cells per high power field. On Oct. 24, 1938, phenolsulphonephthalein test was 22 per cent for two hours. On Oct. 19, 1939, the blood urea was 9.8 and the blood sugar was 105 mg. per 100 c.c. of blood. The blood Wassermann was negative. An electrocardiogram on Oct. 26, 1938, showed no evidence of myocardial disease.

The patient continued to vomit off and on. She was treated with infusions and transfusions. On Nov. 17, 1938, deep x-ray therapy was started. On Dec. 28, 1938, under cyclopropane anesthesia, a hysterectomy and a bilateral salpingo-oophorectomy were performed. The patient's condition was poor following the operation and a transfusion of 400 c.c. of citrated blood was given. On Dec. 31, 1938, she developed a decubitus ulcer. She was given 200 c.c. of citrated blood. Following the operation she was also treated with digalen and other stimulants. Her temperature was septic throughout her stay in the hospital, varying between 98.6° and 103° F. On Jan. 2, 1939, her temperature rose to 109° F., and she died shortly afterwards, five days following the operation.

*Pathologic Report.*—The specimen consisted of a uterus, two tubes, and two ovaries. The uterus was somewhat enlarged and measured 14 by 8 by 4.5 cm. Within the endometrial cavity, in the fundal portion, a large tumor mass was present. The tumor was papillary, friable, and reddish gray in color. It invaded the myometrium for a distance of approximately one-half centimeter. The endometrium immediately surrounding the tumor site was grayish white in color. The rest of the endometrial lining was thick, yellowish in color with areas of congestion. Both tubes were normal in length and showed no gross evidence of metastatic involvement. The right ovary was considerably enlarged and measured 10 cm. in diameter. Numerous cysts were present filled with a yellowish necrotic substance. Some of these cysts contained a papillary-like growth similar to that seen within the uterus.

to be that of malignant invasion. Various stands have been taken in the explanation of the "epidermization" of the endometrium. In 1885, Zeller<sup>9</sup> reported 63 cases of chronic "endometritis" in which he found the single layer of cylindrical epithelium had been replaced by many layers of squamous epithelium. These changes appeared to be due in most cases to long-continued intrauterine applications of iodine, bichloride of mercury or carbolic acid. Gebhard<sup>10</sup> and Flaischlen<sup>11</sup> reported cases where, in long-continued pyometra, the uterine cavity was frequently lined by squamous epithelium. Ries,<sup>12</sup> in 1896, reported a case of chronic inversion of the uterus, in which due to the exposure, dehydration and irritation, the mucosa was lined by squamous epithelium. Senile involution of the endometrium may be a factor in the causation of metaplasia but is an uncommon cause.

Besides these acquired factors, there is also the possibility of an embryonic cause. The highly differentiated epithelial cells found in the various parts of the genital tract are formed from a common type of cell in the Müllerian duct. Thus we have cylindrical, ciliated epithelium in the tubes, the cuboidal, ciliated cell in the corpus, the columnar mucus-producing cell of the cervical canal and the squamous cell type of the pars vagina. Sometimes this squamous variety extends into the cervical canal. Gellhorn<sup>13</sup> suggests that "aberrant" squamous cells may be left in the uterine mucosa or that some undifferentiated cells remain in the uterus and later develop into squamous cells. Natanson<sup>14</sup> found squamous cells in the uteri of the newborn and in infants up to two years of age. Hintze,<sup>15</sup> R. Meyer,<sup>16</sup> Polano,<sup>17</sup> and Sitzenfrey<sup>18</sup> found squamous cell groups in the hyperplastic endometrium and in true adenoma. The possibility that these misplaced cell groups may undergo malignant change is quite conceivable. Goldschmidt<sup>19</sup> and Lissowetsky<sup>20</sup> believe that these tumors develop from heterotopic collections of germinal or Müllerian epithelium. Engellhard<sup>21</sup> does not believe that metaplasia is sufficient to explain the variations in the cellular configurations of endometrial carcinomas. He also favors the embryonic origin. Novak,<sup>7</sup> however, states that he has never observed collections of such cells in the adult uterus and feels that these are lost as a result of the desquamation due to menstruation and pregnancy. He, therefore, concludes that the "epidermization" represents a genuine metaplasia of the cylindrical to the squamous type of epithelium.

Metaplastic changes is not at all uncommon in other parts of the body. Epidermoid carcinoma has been found in the lung, gall bladder, thyroid gland, pancreas, stomach, intestine, and breast. The epithelial cells in embryonal life have the potentialities of forming different types of epithelium, and it is in the basal cells that this potentiality is not lost.

This squamous metaplasia is seen most frequently in adenoacanthoma of the uterus. Gellhorn<sup>13</sup> notes that there have been approximately 25 cases of primary squamous cell carcinomas reported in the literature. There are then the various combinations of squamous and cylindrical cell tumors which are more frequent than the above but are not common. Epithelial pearl formation has been found in this type of neoplasm. Considerable discussion has occurred as to whether this tumor has a double origin or whether it is a squamous transformation in an adenocarcinoma. The latter viewpoint is the one most favorably received at the present time.

#### SUMMARY

Adenoacanthoma is an uncommon tumor of the uterus. This tumor apparently arises as a metaplastic change in the cylindrical cells of an adenocarcinoma of the body of the uterus.

The prognosis in these cases is poor and appears to lie midway between that of a carcinoma of the body of the uterus and a carcinoma of the cervix.

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line incision, 21 cm. in length, extended from the umbilicus to the pubis. The edges of this incision were slightly inflamed. About 100 c.c. of a serohemorrhagic and purulent exudate was found within the peritoneal cavity. In the left lower quadrant of the abdomen, an abscess, measuring 6 cm. in diameter, was situated deep in the muscular wall. The mesenteric lymph nodes were slightly enlarged but showed no evidence of metastasis. The pleural and pericardial cavities revealed no abnormalities. The heart weighed 285 gm. and showed no gross pathologic changes. The right lung weighed 335 gm. and the left lung weighed 260 gm. There were extensive atelectatic areas in the posterior portions of both lower lobes. The bronchial tree was filled with mucus. The spleen weighed 250 gm. The pulp was light red in color, soft, and scraped easily. The splenic corpuscles were obliterated. The liver weighed 1,885 gm. The normal markings were not evident and it was soft in consistency. The biliary tract was normal. The pancreas weighed 130 gm. and showed no gross abnormalities. The left adrenal contained a small adenoma. The right adrenal was normal. The right kidney weighed 160 gm. and the left kidney weighed 165 gm. The capsules stripped with moderate resistance and the gross markings were slightly obscured. The gastrointestinal tract, ureters, and urinary bladder were normal. The uterus, tubes, and ovaries were absent due to operative procedure. No evidence of residual or metastatic neoplasms was found. A culture from the abscess of the abdominal wall revealed *B. coli* and *Staphylococcus aureus*.



Fig. 3.

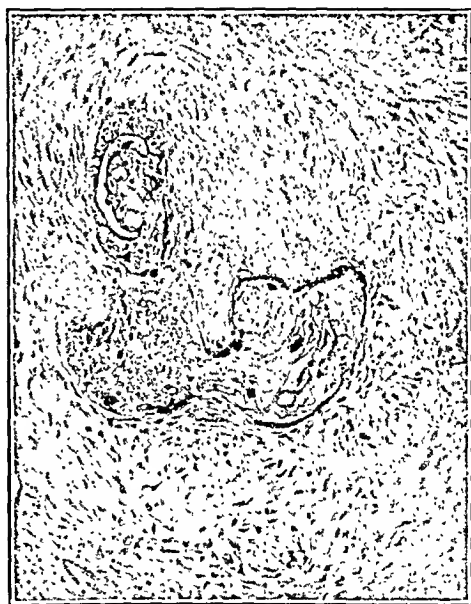


Fig. 4.

Fig. 3.—Metastatic tumor in ovary of typical cylindrical cell type.

Fig. 4.—The metaplastic change of squamous epithelium from the cylindrical epithelium is indicated in this section.

#### DISCUSSION

Since squamous cell carcinoma cannot arise directly from cylindrical epithelium, this latter type of tissue must undergo a transformation into pavement epithelium. This "epidermization" of the endometrial epithelium, according to Novak,<sup>7</sup> may be seen infrequently in benign lesions. This change may occur in either the surface epithelium or in the glands and is more common in the latter. Meyers<sup>8</sup> states that most frequently the squamous cell groups will project into the lumen of the gland in a glomerulus-like manner. It is also likely that when the endometrium projects into the muscular wall, the metaplastic changes may produce a picture which appears

The product used in this study was standardized by the Allen-Doisy method, and when standardized in this manner, 1 mg. of stilbestrol was found to have the same activity as 25,000 I.U. of estrone.<sup>6, 9</sup> Dodds, Lawson, and Noble<sup>6</sup> found diethylstilbestrol to be approximately two and one-half times as potent as estrone in producing vaginal estrus in ovariectomized rats, and that the compound definitely stimulated uterine growth. The latter property has also been observed in the human being.<sup>2, 4</sup>

Stilbestrol possesses other properties characteristic of natural estrogens as evidenced by its power to suppress the production of the anterior pituitary gonadotropic and growth hormones,<sup>7</sup> its capacity to suppress the action of progestin,<sup>8</sup> its adverse effects upon lactation,<sup>5, 8</sup> and its ability to sensitize the uterus of immature rabbits to progesterone.<sup>6</sup> The effect of this synthetic estrogen on breast tissue is similar to that of estrone but much less marked.<sup>6</sup>

Studies in toxicity<sup>9</sup> "indicate a broad margin of safety between the toxic and the effective dose for the laboratory animal. The intravenous lethal dose for the cat (the lowest for any animal tested) is 30 mg./Kg."

#### MATERIAL

Our clinical material consists of 50 cases from the Hutchinson Memorial Clinic of Tulane University of Louisiana, and the private practice of one of us (C. G. C.). In this group of 50 patients, there were 19 classed as having a physiologic menopausal syndrome (Group I). Sixteen patients had postoperative or postradiation menopausal syndromes (Group II), while 13 cases were classified as manifesting hypoestrinism (Group III). In addition there were two cases of senile vaginitis.

#### GROUP I. PHYSIOLOGIC MENOPAUSAL SYNDROME

The physiologic menopausal syndrome group contained 19 patients ranging in age from 30 to 55. Their complaints included various combinations of the following symptoms: Headache, dizziness, nervousness, hot flushes, depression, muscle and joint pain, frigidity, insomnia, vaginitis and irritability. One patient in this group had diabetes insipidus as a complicating factor.

The same method of individualized treatment outlined for the previous group was followed. However, it was found necessary to employ larger dosage in some of the younger members of this group to maintain a satisfactory control of symptoms.

The therapy in this group was individualized in accord with the severity of the presenting symptoms. Early in the series we gave injections of 1 mg. (25,000 International Units) once or twice weekly, but later it was found more efficacious to start with a large initial dose of 5 mg. (125,000 I.U.), decreasing the amount administered as the symptoms were controlled. More recently, we have substituted oral administration when the symptoms were adequately alleviated by intramuscular therapy. It was found that successful oral administration required approximately three times the quantity previously given by the intramuscular route.

#### GROUP II. SURGICAL MENOPAUSAL SYNDROME

There were 16 patients ranging in age from 20 to 60 years in this group. The interval between operation or irradiation and the inauguration of stilbestrol therapy varied from three months to twenty-five years. Likewise the symptoms varied in number and intensity, and included the following: nervousness, dizziness, flushes, headache, depression, muscle and joint pain, frigidity, insomnia, vaginitis, pruritus, weakness, and irritability. One patient in this group had diabetes insipidus as a complicating factor.

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## CLINICAL EXPERIENCES WITH STILBESTROL (DIETHYLSTILBESTROL)

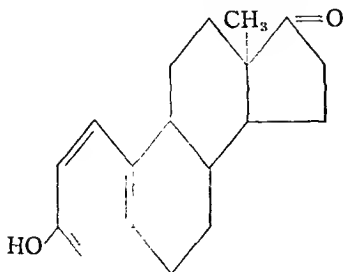
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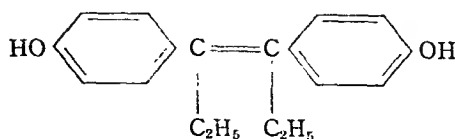
IN 1938 Dodds<sup>1</sup> and his associates introduced a new synthetic preparation with effective estrogenic properties, 4-4' dihydroxy a.b. diethyl stilbene for which the name diethyl stilbestrol was proposed and later abbreviated to stilbestrol. Reports in the foreign literature, particularly the British,<sup>2-5</sup> seem to indicate that this substance possesses estrogenic activity comparable if not superior to the biologic estrogens in vogue in the United States.

Because of its availability with as many as 125,000 international units per c.c., its previous clinical acceptability abroad and its relative economy, we were led to utilize this drug\* in a series of cases in which estrogenic therapy was indicated.

Stilbestrol can be easily synthesized and does not contain the phenanthrene nucleus formerly thought to be an essential component of an estrogenically active substance.



Estrone



Diethylstilbestrol

\*We wish to express our appreciation to the Winthrop Chemical Company for supplying us with the diethylstilbestrol used in these cases.



in muscle and joint pain and frigidity is not as impressive as the effectiveness of this synthetic estrogen on the other symptoms, but is as good as we have previously obtained with biologic estrogens.

It is interesting to note that 16 of these patients had previously received estrogenic therapy with biologic preparations, the total dosage ranging from 12,000 to 125,000 I.U. Of these, 13 were relieved of their symptoms and were maintained satisfactorily when stilbestrol was substituted. Three patients of this group obtained no relief from their previous therapy, and of these, 2 were completely relieved by stilbestrol, the third showing only slight improvement.

#### TOXIC EFFECTS

In this series no patient completely intolerant to stilbestrol was encountered. Approximately 60 per cent of the patients complained of nausea at some time during the treatment, an observation also made by others.<sup>3-5, 10</sup> The nausea was usually mild and transitory in nature, and was successfully relieved by decreasing the dosage, and very frequently did not recur despite the continued use of the same quantity which previously invoked nausea. When nausea followed oral administration, it was frequently lessened or relieved by changing to intramuscular injection. It has been our experience that patients are more tolerant to intramuscular than to oral administration of the drug.

In only one case was the nausea sufficiently severe to cause cessation of therapy for the period of a week, following which therapy was resumed without untoward effect. In one case a dermatitis appeared which may possibly be attributable to stilbestrol. In a new series of patients to whom the stilbestrol is to be administered solely per os, sodium bicarbonate will be given in 4 gm. doses simultaneously. Our experience indicates that the concurrent use of sodium bicarbonate with stilbestrol seems to lessen nausea.

#### RECOMMENDATIONS

Our observations regarding the administration of stilbestrol where estrogenic therapy is indicated lead us to suggest that: (a) therapy be individualized; (b) the initial administration be by the intramuscular route and preferably in large doses (5 mg. once or twice weekly); (c) when symptoms are controlled the dosage may be reduced to 1 mg. once or twice weekly; (d) a patient adequately maintained on such dosage may have oral administration substituted for intramuscular; (e) the dosage for oral therapy should be successful if given in a quantity equivalent to three times the previous intramuscular administration; (f) when oral administration is utilized sodium bicarbonate should be administered concomitantly.

#### CONCLUSIONS

1. The pharmacology, physiology, and toxicity of a new synthetic estrogen, "stilbestrol," containing 25,000 I.U./mg. is discussed.

2. Our experience in 19 cases of physiologic menopausal syndrome, 16 cases of surgical menopausal syndrome, 13 cases of hypoestrinism and 2 cases of senile vaginitis is presented.

3. The results indicate that these types of cases may be satisfactorily controlled with this new synthetic estrogen as efficiently as with the available biologic estrogenic substances and stilbestrol is recommended because of ease of administration, relative low cost, and the wide range of utility.

4. Oral administration of stilbestrol has yielded satisfactory results in those patients to whom it has been given. We are presently extending our observations on this mode of administration.

## GROUP III. HYPOESTRINISM

There were 13 patients in this group, ranging in age from 21 to 36 years, and manifesting symptoms attributable to estrogenic insufficiency. The complaints presented by these patients included nervousness, dizziness, flushes, headache, depression, frigidity, insomnia, and irritability, especially marked at the menstrual period. In addition, two patients complained of dysmenorrhea, one of hypomenorrhea, and one patient had peripheral edema associated with the menstrual period. The patients with dysmenorrhea were markedly improved and the patient with menstrual edema obtained prompt relief. The effectiveness of stilbestrol therapy in the remaining members of this group is indicated in Table III.

Again the therapeutic regime employed was similar to that previously discussed, in that each case was individualized and the dosage varied according to the severity of the symptoms. Here, however, the drug was administered according to that time of the menstrual cycle at which the symptoms appeared. In general, smaller dosages sufficed to eradicate adequately and to alleviate symptoms. Usually 5 mg. were given intramuscularly approximately two days before the periodic onset of symptoms.

TABLE I. SURGICAL MENOPAUSE, 16 CASES

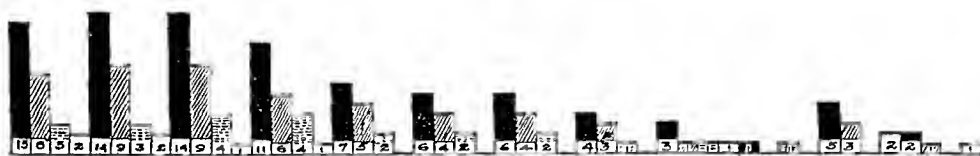


Table II. Physiological Menopause, 19 Cases

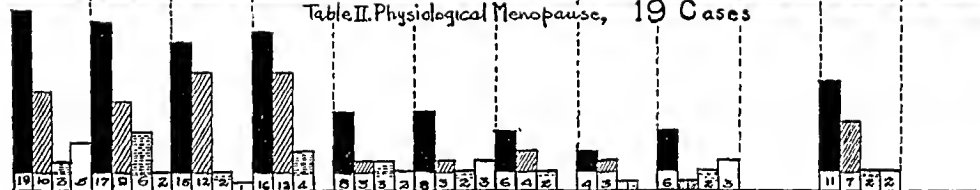
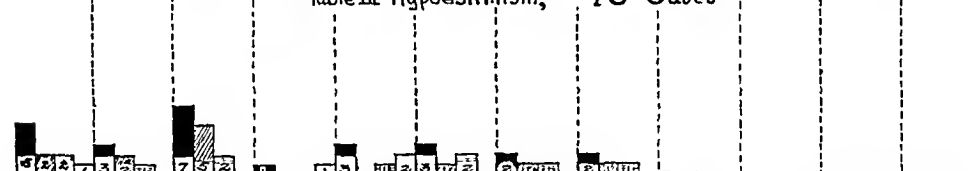


Table III. Hypoestrinism, 13 Cases



■ Column I. Frequency.  
 ▨ Column II. Complete Relief.  
 ▤ Column III. Improvement.  
 □ Column IV. Unimproved.

## SENILE VAGINITIS

In our series there were 2 cases in which senile vaginitis was the only complaint. These were promptly relieved by stilbestrol given intramuscularly in dosage of 5 mg. once weekly. The patients' reports of symptomatic improvement were concurrent with the finding of increased cornification as evidenced by vaginal smears.

## RESULTS

Tables I, II, and III summarize in detail the results obtained in the three larger groups of patients treated with stilbestrol. One can observe at a glance that the more frequent and disturbing symptoms, such as headache, nervousness, dizziness, and hot flushes, are successfully relieved in a large and gratifying percentage of cases. We were pleased to observe that patients frequently reported relief of symptoms very shortly after the inauguration of therapy. The improvement that stilbestrol yields



Fig. 1.—Initial biopsy. A conglomeration of cervical glands, showing variable degrees of hyperplasia, squamous metaplasia, secretory activity and disorganization, are supported by a stroma consisting almost entirely of hyalinized connective tissue. About 50 per cent of the tissue is hyaline, which stains characteristically by the Van Gieson technique. Mucus and neutrophils occupy the gland lumens.

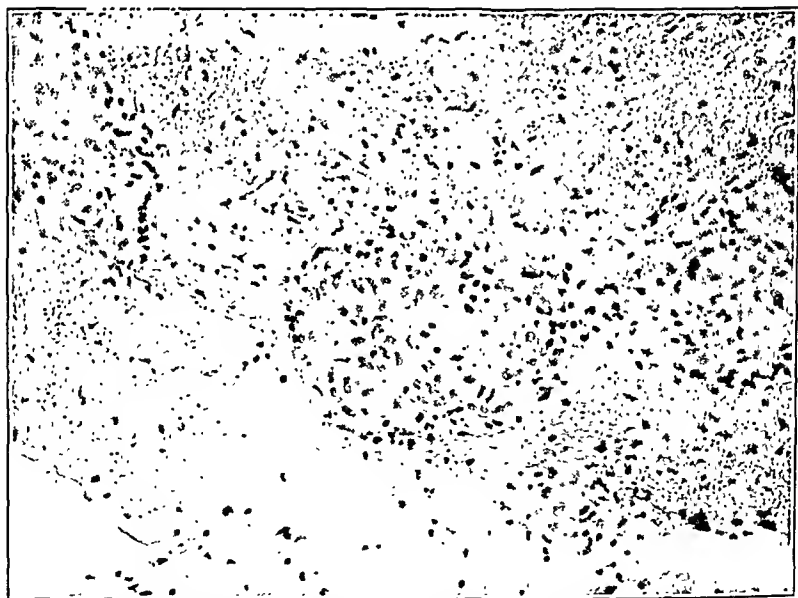


Fig. 2.—Hyaline adenoma of cervix (hematoxylin and eosin). Third biopsy. (Two and one-half years after initial biopsy. Magnification twice that of Fig. 1.) Recurrence of the original cervical tumor. No glandular elements could be found. Small islands of somewhat hyperplastic squamous epithelium are imbedded in hyalinized connective tissue, and are derived from glandular epithelium which has undergone squamous metaplasia. This recurrence occurred one inch above the external os in the cervical canal.

A biopsy six months before this had shown a marked increase in the hyaline stroma, disintegration of glandular structures, areas of vascular granulation tissue surrounded by hyaline, and surface sloughing. Squamous epithelium at that time was scant and hydropic, showing both intracytoplasmic and intranuclear edema.

The most recent biopsy, ten months after the third, has shown little change other than further increase in the hyaline reaction with less squamous epithelium.

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## HYALINE ADENOMA OF THE CERVIX

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SEVERAL months ago a specimen of cervical tissue was examined which presented a puzzling and unique histologic pattern. According to the history, a diagnosis of adenocarcinoma of the cervix had been made two years before, and a supracervical hysterectomy performed. Upon examination of the uterus after its removal, no tumor could be found, but a deep longitudinal groove was noted in the lower segment, which was regarded as the probable source of the material obtained for biopsy, and it was assumed that the tumor had been completely removed by the curette. During the interval of two years nothing unusual had been observed in the cervical stump, until the development of a soft, diffuse, polypoid formation, extending about an inch up into the cervical canal, had prompted the removal of the specimen just mentioned for further examination. The specimen was compared with that examined two years before, and the patterns of the two were found to be essentially alike.

Since the biology of this tumor and the unusual histologic pattern made it inadvisable to diagnose the tissue as malignant, the descriptive term "hyaline adenoma" was adopted. A search of the files back to 1928 disclosed two other tumors of a similar character, but lacking the hyaline stroma, both of which had been classified as adenocarcinoma of the uterus. The clinical records of, and meticulous histologic study of, the tissue removed from the three patients clearly show that these tumors are not cancer.

The first patient was a 27-year-old woman, married for two years, obese, always regular in her menses, and who had had a cervical discharge for ten years. When she finally consulted a regular physician after years of osteopathic treatment for back pain, a polypoid formation extending high in the cervical canal prompted the biopsy, which resulted in the diagnosis of adenocarcinoma and the supracervical hysterectomy just described. Fig. 1 shows the pattern of the cervical tumor found in the initial biopsy. The hysterectomy without removal of the cervix afforded an excellent opportunity to study the biology and subsequent progress of this tumor. Two years later, as described in the first paragraph, the second biopsy was made; six months later, the third, which is shown in Fig. 2, and after another interval of ten months, a fourth biopsy. No evidence of malignancy ever developed from a clinical point of view. The second biopsy specimen is not presented because of poor contrast for microphotographic work, but in it the glandular elements had almost disappeared, and between the hyaline islands vascular granulation tissue and pale hydropic squamous epithelial cells, showing both intracytoplasmic and intranuclear edema, were the essential features. It is to be noted that in the third biopsy the epithelial islands were quite healthy and distinct. The latest biopsy has shown no significant change during the past ten months, and the squamous epithelium is less prominent.

The second patient, a 40-year-old woman, obese, married three years, and never pregnant, was also subject to back pain. Her periods had always been profuse,

cervical glands,<sup>1</sup> and Oppenheimer,<sup>2</sup> in 1932, reported a diffuse polypoid hypertrophy of the cervical mucosa in the nulliparous cervix.

Since the first patient with the hyaline adenoma had had a cervical discharge for ten years, and since the glandular patterns of the lesions of the others are very similar, but lacking the hyaline stroma, it is possible that their shorter duration without prolonged inflammatory irritation may explain the absence of the hyaline. Neither of these two lent themselves to the follow-up study possible with the first.



Fig. 4.—Adenomatoid hyperplasia of cervical glands. (Hematoxylin and eosin.) This specimen perhaps represents the youngest form of the process terminating in hyaline adenoma, and is typical of an inflammatory reaction in glandular polypoid tissue, with marked multiplication of the glands and a tendency to squamous metaplasia, warranting its inclusion in this series. Neutrophile infiltration is marked in the stroma and gland lumens. Hyalinization is not present. Endometrium accompanying the cervical curettings showed the early follicular phase.

#### SUMMARY

A tumor of the cervix, termed hyaline adenoma, the evolution of which has been observed *in situ* for over three years, is described. Two other lesions simulating it, but lacking the hyaline stroma, are also presented. The study of the life cycle of the hyaline adenoma has shown that its first stage consists of a proliferation of small, dilated and cystic cervical glands enclosed in a dense hyaline stroma which comprises about 50 per cent of the microscopic fields, and in which the glandular epithelium is disorganized and shows considerable squamous metaplasia. Subsequent biopsies exhibit disintegration and disappearance of the glands and the development of small islands of squamous epithelium with further proliferation of the hyaline stroma in which they are imbedded, but manifesting no evidence of malignancy.

The two lesions presented as similar to the hyaline adenoma and tentatively regarded as its possible precursors, would be more properly classified as adenomatoid glandular hyperplasia. These entities are believed to be of inflammatory origin, thus far reported only in the cervix of nulliparous women.

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and for the preceding three years irregular and lasting from sixteen to twenty days. Both her mother and sister had menstruated regularly throughout their pregnancies. Three years ago the cervix and uterus were curetted, and a laparotomy performed, although only the appendix and an ovary were removed, because the uterus appeared normal. The curettings were reported as adenocarcinoma of the cervix (Fig. 3) by two pathologists, and irradiation was administered to the uterus and cervix. Another biopsy, made just before irradiation treatment was begun, showed only a low grade, chronic inflammatory reaction with no evidence of remnants of the original tumor. Management was based upon the tissue obtained in the original curettage. No further abnormalities developed, and for the past three years she has been regarded as cured.



Fig. 3.—Adenoma of cervix without hyaline stroma. (Hematoxylin and eosin.) The glandular pattern of this tumor so closely resembles that of the hyaline adenoma, shown in Figs. 1 and 2, that it seems allied to it. Here the stroma is scant, but without any hyalinization. Gland septa have broken down, and the confluence of the glands has produced a diminutive cystadenomatous formation. Many glands are cystic, and neutrophils are present in their lumens. Endometrium present in the curettings showed the pathologic follicular phase, with cystic and dilated glands. Mucicarmine stains demonstrated an abundance of mucus in the cells and lumens of the cervical glands.

The third patient, a 42-year-old woman, underwent a panhysterectomy for fibroids, but died forty-eight hours after the operation. Besides multiple intramural leiomyomas, the uterus presented rough, granular, shaggy tabs involving the mucosa of the lower segment and cervical canal, which on histologic examination invited the diagnosis of low grade adenocarcinoma (Fig. 4). Menorrhagia and metrorrhagia had developed five months before operation, with back pain and low abdominal cramps, prior to which she had experienced no abnormalities. Early menopausal symptoms were also noted. She had been married since the age of 17, and one abortion eighteen years before admission constituted the only pregnancy.

Because of the unusual interest of the first of these three lesions, and since all three types are undoubtedly being encountered from time to time, it is felt that the presentation of these three cases will be of interest. I can find in the literature no reference to the pathologic entity which I have described as a hyaline adenoma, but the other two are occasionally mentioned as adenomatoid hyperplasias of the

At operation the abdomen was full of blood, part of which was fresh and unclotted, while many dark clots were also present. The uterus appeared slightly enlarged. The pelvic peritoneum and pelvic viscera were congested. Numerous fibrous pelvic adhesions were present. The right tube was thickened but its ostium was patent. The distal portion of the left tube was embedded in a mass of blood clot. This portion of the tube was grossly enlarged and had ruptured. Blood was oozing from the rupture and grayish villous tissue was protruding through the break in the wall of the tube. The condition was obviously a ruptured tubal pregnancy. Both ovaries appeared essentially normal. The left tube was removed. The fetus itself was not observed. Tuberculous salpingitis was not suspected at the time of operation. For two days postoperatively the patient's temperature rose to 103° F. and her pulse rate to 120. Then gradually both returned to normal. Four days after operation she expelled a piece of tissue which on microscopic study proved to be a decidual

Fig. 1.

Fig. 2.

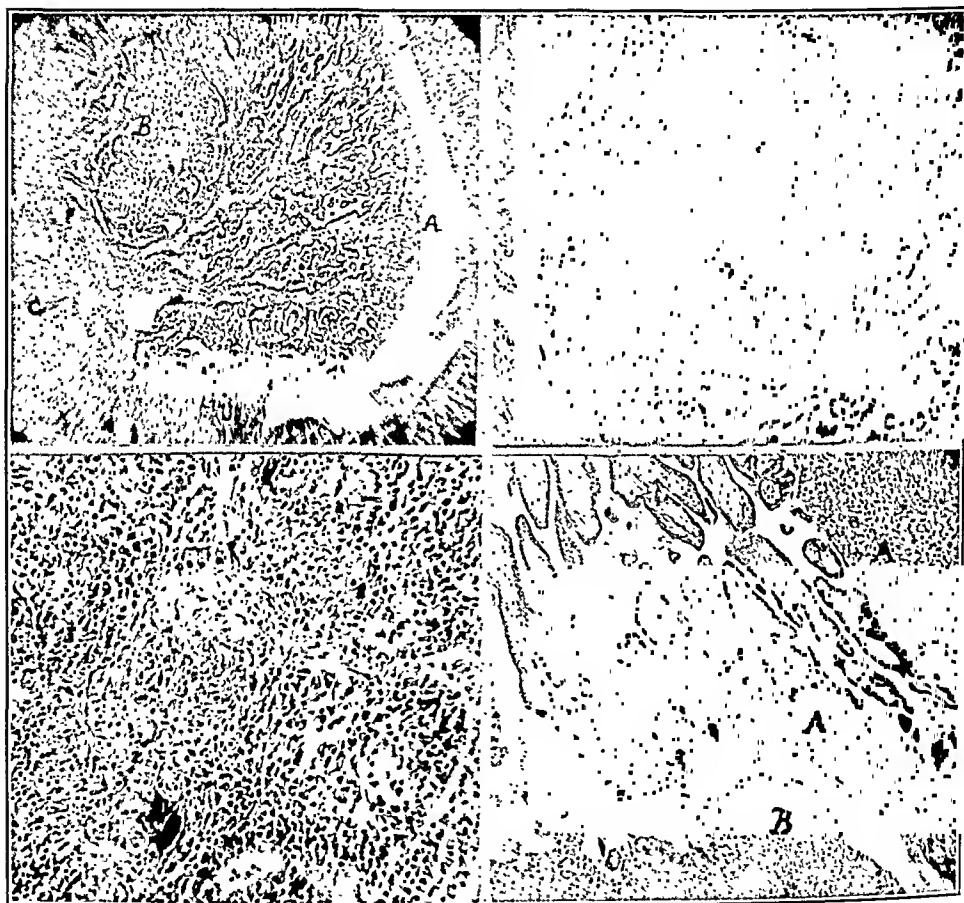


Fig. 3.

Fig. 4.

Fig. 1.—Section across the tube proximal to the pregnancy. Note the matting together of the mucosal folds forming pseudoglandular spaces. A indicates the lumen; B, a tuberculous area; and C, the wall of the tube. (X36.)

Fig. 2.—An enlarged view of area B, showing conglomerate tubercles with two giant cells. (X72.)

Fig. 3.—High power view of tuberculous area B. Note the numerous lymphocytes and plasma cells and two giant cells. (X230.)

Fig. 4.—Section across the ampullary portion of the tube showing the pregnancy. Syncytial knots, masses of trophoblastic epithelium and numerous well-formed chorionic villi are shown. A indicates areas of trophoblastic epithelium (Langhans' cells). B is a mass of blood clot. (X72.)

## TUBAL PREGNANCY ASSOCIATED WITH TUBERCULOUS SALPINGITIS

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TUBAL pregnancy associated with tuberculous salpingitis is a very rare occurrence. Recently Stevenson and Wigerton reported such a case, believed to be the first reported from the English-speaking world.\* They have reviewed the literature and found only eight proved cases. For a summary of these cases the reader is referred to their article.

We desire to record another case of coincidental tubal pregnancy and tuberculous salpingitis, apparently the first to be reported from Canada and the third from the English-speaking world.

Mrs. K. H., white, aged 32 years, married five years, no previous pregnancies, was admitted to Victoria Hospital Feb. 17, 1939, and was discharged on March 7, 1939.

*Past History.*—The patient was born in England and came to Canada at the age of six years. She has had no serious or significant illnesses, no operations and in general has enjoyed reasonably good health. She was never suspected of having tuberculosis. Five years ago she was told that she had a gastric ulcer but this diagnosis was never proved, and she is now free from gastric symptoms. For two years she has frequently suffered from crampy lower abdominal pains, midline and in both lower quadrants, more severe a week before and just after her menstrual periods. Her menstrual cycle has been regular every twenty-eight to thirty days, moderate flow lasting three to four days with severe pain during the first day, no intermenstrual bleeding, no periods of amenorrhea prior to the present pregnancy.

*Present Illness.*—The patient's last normal menstrual period was on Dec. 25, 1938 but between that date and Jan. 25, 1939 she had a small amount of spotty vaginal bleeding. After January 25 the spotting stopped and some morning sickness and vomiting commenced. Her breasts became quite sore and enlarged. She believed that she was pregnant. All during this time the lower abdominal pain, which she had experienced for two years, was still present. About Jan. 25, 1939 she consulted her doctor for this long-standing abdominal pain. Pelvic examination was difficult and quite unsatisfactory, due to tenderness and a small introitus. Between Feb. 3, 1939 and Feb. 17, 1939 the patient had three attacks of severe lower abdominal and pelvic pain, lasting two to three hours. During the first attack she vomited but no vomiting took place in the two subsequent ones. The pelvic organs were tender and painful. After the second attack she felt very weak but did not faint. On the day of admission (Feb. 17, 1939) the third attack of severe abdominal pain began at 6 p.m. The pain was crampy, situated about  $1\frac{1}{2}$  inches below the umbilicus and lasted two to three hours. She was brought to the hospital by ambulance at 11 p.m. All during this time after Jan. 25, 1939 there was no vaginal bleeding. On admission her temperature was  $100^{\circ}$  F., pulse 80, hemoglobin 75 per cent, white blood cell count 13,650. Pelvic examination revealed a slightly enlarged uterus with a softened cervix. No blood was present on the examining fingers. The abdomen was tender throughout but not rigid and no masses could be detected. Operation was performed at 3 a.m. on Feb. 18, 1939.

\*Since this paper was submitted, our attention has been called to the report of another case by Dr. Arthur Stein of Chicago (see reference).



## CARCINOSARCOMATODES OF THE UTERUS\*

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CARCINOMA of the uterus, while not a rare condition, occurs but once among each 670 women registering at the Mayo Clinic. Sarcoma of the uterus, on the other hand, is rare, accounting for only 2.5 per cent of malignant lesions of the uterus. The coexistence in the same uterus of two tumors, one an adenocarcinoma, the other a sarcoma, is an unusual coincidence, having been reported in about twenty instances only. Carcinosarcomatodes of the uterus is the term used to designate a single neoplasm, having the morphologic features of carcinoma and sarcoma. The entire literature on this pathologic curiosity consists of six individual case reports.

### HISTOGENESIS

Sarcoma of the uterus may arise in the myometrium or in the endometrium. In the myometrium it may be primary or originate in a pre-existing leiomyoma. Theoretically it might arise from smooth muscle tissue, connective tissue, or endothelium of blood vessels. Many authorities, among them Ewing, have expressed the belief that all sarcomas of the myometrium are of myogenic derivation. Sarcomas of the endometrium are always primary and are generally conceded to be derived from the stromal cells. Adenocarcinoma of the fundus of the uterus is derived from the endometrial glands.

The histogenesis of carcinosarcomatodes is not at all well understood. Ewing summarized the existing theories as follows: (1) A carcinoma and a sarcoma begin as separate tumors and later one invades the other. (2) At the point where a sarcoma reaches the endometrial surface, a carcinoma develops secondarily. (3) A common irritant produces neoplasia of both epithelial and connective tissue elements.

### PATHOLOGY

Sarcoma of the endometrium occurs in two forms: the polypoid and the diffuse; no cases of carcinosarcomatodes of the latter type have been described. The lesions are vascular with a smooth surface as contrasted with the shaggy appearance of adenocarcinoma of the uterus. For the sarcoma, round, oval and spindle-cell varieties, alone or mixed, have been described. Giant cells have been encountered occasionally. Mitotic figures and other features of malignancy are present. The blood vessels are numerous, thin-walled and occasionally are invaded by sarcoma cells. Evans has derived a mathematical formula for the activity of growth of uterine sarcoma; he based his data on the number of mitotic figures per cubic millimeter of tumor tissue. He found a direct relation between the number of mitotic figures and the duration of life after operation. The carcinomatous portion of the lesion manifests itself by atypical glandular proliferation in the depths of the polyp or on the free surface of the latter, as in the case we are about to report. Multiple mitotic figures, prominent nucleoli and lack of differentiation are usually marked features. The relative malignancy of these lesions cannot well be determined because of insufficient data on the small number of cases reported. However, we do know that primary uterine sarcoma is much more malignant in its course than the so-called secondary variety. Kimbrough stated that three-year cures were obtained in 15 per cent of the cases of primary uterine sarcoma. In contrast to this, Masson reported 70 per cent

\*Submitted for publication, July 1, 1939.

cast. Otherwise her postoperative convalescence was uneventful and she was discharged from the hospital in good condition.

*Pathologic Report.*—The left tube measured 6 cm. in length. The narrow proximal segment measured 1.5 cm. in its greatest diameter. Its wall was somewhat thickened, its lumen slightly dilated and its mucosal folds were edematous. The ampullary segment was embedded in a mass of blood clot which, when gently lifted and partially dissected away, revealed a friable villous tissue and a small gestation sac which was ruptured and empty. The gestation products and blood clot were protruding through a gross rupture in the wall of the tube. The fimbriae were little distorted and the abdominal ostium of the tube was patent. Tuberculous salpingitis was not suspected until the microscopic sections were seen.

Microscopic sections through the isthmus and the ruptured ampullary portion were studied. The latter portion showed masses of fresh and older blood clot, numerous well-formed and well-preserved chorionic villi and syncytial masses (Fig. 4). The mucosa of the tube was destroyed at this level. The wall of the tube was much thinned out, moderately edematous and infiltrated with lymphocytes. The trophoblastic epithelium was active and had infiltrated deeply into the wall of the tube where there was also a moderate decidual reaction. In the section through the isthmus most of the plicae were fused together forming pseudo-glandular spaces containing blood and desquamated epithelial cells (Figs. 1 and 2). The stroma of the plicae, the submucosa, and wall of the tube were heavily infiltrated with lymphocytes (Figs. 2 and 3). The wall of the tube was not thickened. Its muscularis seemed to be deficient. Numerous discrete and conglomerate tubercles were situated in the plicae, submucosa and in the subserous tissue of the tube. Some of these possessed central giant cells and the larger tubercles showed caseous centers (Fig. 3). Vascular fibrous adhesions were attached to the serous surface of the tube. The pathologic diagnosis was: ruptured tubal pregnancy (left) associated with tuberculous salpingitis.

#### COMMENT

It is probable that this patient suffered from tuberculous salpingitis and pelvic peritonitis for quite a long period of time, as the history of lower abdominal and pelvic pain for at least two years suggests. The history of five years' sterility might also be explained on this basis. At the present time (June 26, 1939) the abdominal wound has completely healed, the patient's weight has returned to normal and she is menstruating regularly. Tubal pregnancy was made possible through the patency of the abdominal ostium which is so often sealed off in the usual case of tuberculous salpingitis. The probable explanation for the remarkable infrequency of coincidental tubal pregnancy and tuberculous salpingitis has been adequately discussed by Stevenson and Wharton. In the cases which have been reported the condition occurred more commonly in the left tube. This also applies to our case. It is also noted in our case that pregnancy occurred in the lumen of the tube closely adjacent to the tuberculous process as also happened in four of the reported cases, rather than at the ostium, or attached to the fimbriae or an ovary.

#### REFERENCE

Stevenson, C. S., and Wharton, L. R.: *AM. J. OBST. & GYNEC.* 37: 303, 1939.

in the right shoulder. One month later numbness was noticed in the lower extremities. This numbness had gradually "ascended" to involve the entire surface of the body below the line of the clavicle. Physical findings were those of a transverse myelitis at the level of the first thoracic vertebra with sensory and motor paralysis, below the lesion. Roentgenologic examination of the spinal column gave negative results but spinal puncture revealed a complete spinal subarachnoid block.

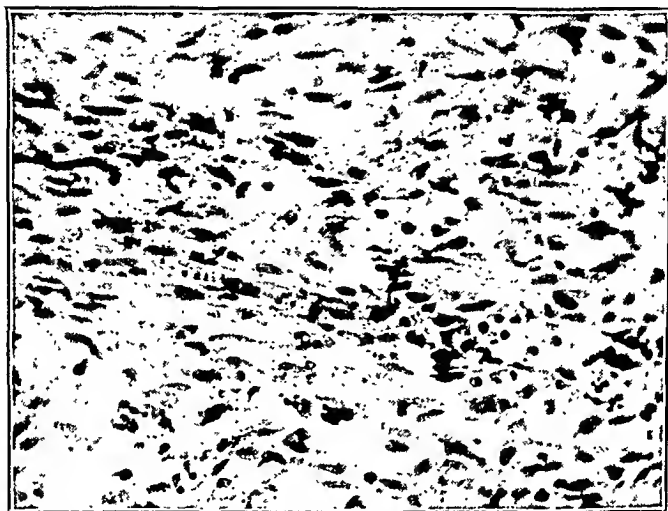


Fig. 1.—Section from operative specimen of tumor of spinal cord, showing a metastatic fibrosarcoma; one may note absence of carcinomatous elements ( $\times 240$ ).

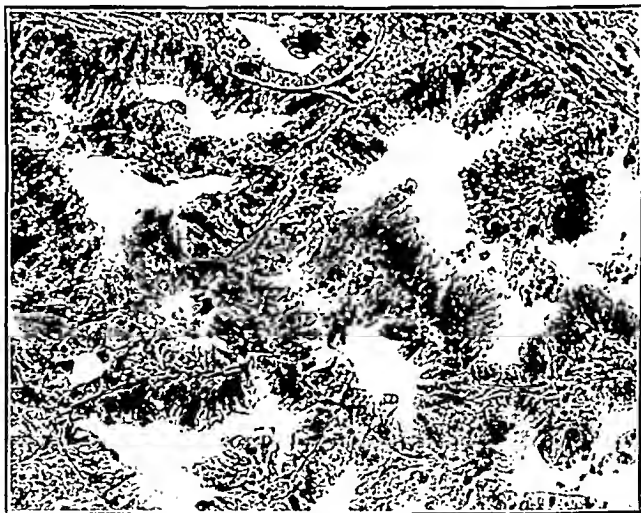


Fig. 2.—Uterine polyp showing carcinomatous element ( $\times 200$ ).

At operation on March 15, 1939 Dr. Adson performed a laminectomy and curetted away from the first thoracic lamina, a tumorous mass of tissue that was found to be compressing the spinal cord. Microscopic examination of the tissue removed revealed a fibromyxosarcoma (Fig. 1). Following operation, some subjective relief was temporarily obtained, and a course of roentgen therapy to the spinal column was begun. This had to be discontinued because of persistent nausea. Rapid failure ensued with abdominal distention, weakness and drowsiness, and death occurred on April 17, 1939. Necropsy disclosed widespread skeletal and visceral metastases of sarcomatous type.

of cures in a series which included mainly sarcoma originating in fibroids. It is evident, therefore, that the prognosis is three or four times better in the secondary than in the primary type, which includes the tumors under consideration.

### CLINICAL FEATURES

The clinical features of carcinosarcomatodes are not characteristic. Most of the recorded examples occurred among nulliparous patients after the menopause; a similar observation was made in cases of endometrial sarcoma. Bleeding was a constant feature and appeared to be more persistent and profuse than in cases of carcinoma of the fundus of the uterus. There were no other noteworthy features.

In 1932 it was stated by Wolfe that a diagnosis of endometrial sarcoma is made from endometrial scrapings in about 50 per cent of the cases.

### REPORT OF A CASE

A married, white nullipara, aged 29 years, first registered at the clinic Feb. 8, 1923. An operation for perirectal fistula was performed. Her family history and personal history were not significant. Appendectomy had been performed five years previously. Menses were recorded as being regular and normal. Between the years 1923 and 1928 she was seen at the clinic on several occasions and received treatment for pulmonary tuberculosis with good result. On her fifth visit to the clinic, Oct. 1, 1934, her complaint was menorrhagia of six months' duration, which was associated with prolonged menses. For two months drainage of a brownish material had occurred intermenstrually. Dilatation and curettage was carried out Oct. 4, 1934, and the patient was given a half of a menopausal dose of radium. The pathologic diagnosis from the scrapings was endometritis.

On April 22, 1938, the patient again returned to the clinic complaining of a bloody vaginal discharge which had been present continuously for three weeks. There had also been pain of intermittent character in the right lower quadrant of the abdomen and in the lumbar region. She attributed her present complaints to an automobile accident which had occurred immediately prior to the onset of the vaginal bleeding.

Physical examination gave essentially negative results except that a small polypoid-appearing mass about 2 cm. in diameter was presenting at the external os. It had the glossy appearance of placental tissue. The possibility of an incomplete miscarriage was considered, but the cessation of menstruation two years prior to this time made pregnancy only a remote possibility.

April 23, 1938, the cervix was dilated and a curettement of the uterine cavity was carried out. Microscopic examination of the tissue removed revealed fibrosarcoma. Hysterectomy was advised but because of the patient's indecision it was delayed three weeks. On May 13, a radical total abdominal hysterectomy with removal of both tubes and ovaries was performed. The abdominal exploratory procedure did not reveal any abnormality except that the gall bladder was thin walled and contained multiple stones. There was no noticeable change in the lymph nodes indicating spread of the malignant process. An uneventful convalescence followed and the patient was able to be dismissed from the hospital on the twelfth day after operation and from the clinic on the seventeenth day.

Study of the organs removed revealed both tubes and ovaries to be normal. The uterus measured 6 by 5 by 4 cm. and contained multiple mural leiomyomas measuring as much as 3 cm. in diameter. On the endometrial surface, immediately above the internal os, there was a sessile polyp about 5 mm. in diameter which was soft and smooth; on section, it proved to be very vascular. Microscopically it presented the unusual combination of sarcoma and carcinoma. No other lesions were in evidence in the endometrium, which grossly was atrophic.

On her last admission, March 3, 1939, the patient stated that she had been well for eight months following her last operation. On Jan. 10, 1939, there had suddenly developed pain in the region of the left shoulder; the pain had extended down the left arm. Ten days later pain of a similar character and distribution developed

tion. Sections through the fibromyomas revealed no evidence of sarcomatous transformation. The tubes and ovaries were not unusual microscopically.

### COMMENT

Hysterectomy was indicated when the presence of a malignant lesion was established at the time of curettement. In instances in which the procedure cannot be carried out immediately, as in this case, it is the experience of one of us (Dixon) that hysterectomy should be delayed several days rather than two or three days following curettement, the reason being that the lymphatics surrounding the cervix are apparently the site of origin of an infectious process which may result in extensive and fatal peritonitis if hysterectomy is performed too soon after curettement. Therefore, the belief is here expressed that if hysterectomy is indicated after curettement and it cannot be carried out immediately, which is the ideal time, then it should be delayed for at least ten days for the purpose of allowing any infectious process in and around the cervix and uterus to subside.

Pathologically this case is of exceptional interest because of the unusual "mixed" character of the malignant lesion. The "selective" nature of the metastasis, in which sarcoma alone was found, indicates that the sarcoma had metastasized by the blood stream before the carcinoma had begun to spread. This observation is in keeping with the relative activity of these two types of malignant lesions in connection with the endometrium.

So far as we know this is the seventh case of carcinosarcomatodes to be reported in the literature.

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During the last few years there has been described a particular affection of the skin of the newborn. It is more commonly designated as benign subcutaneous induration of the newborn, or pseudoscleroderma.

It is characterized by zones of cutaneous infiltration varying in size from a small nodule to an area as large as the palm of the hand. The areas are slightly elevated, irregular, and of a deep wine red color. They show a ligneous resistance, and prolonged pressure will not cause pitting. The surface at times resembles that of a lemon peel. The condition successively regresses; the color becomes paler and the zone of induration reduces in extent until it entirely disappears.

These infiltrations appear immediately after delivery or within a few days after, rarely after the second week. Sites of predilection are in the regions of the face, deltoids, back, and buttocks.

The disease may last from a few weeks to a few months, always ending in a spontaneous cure. Progress and growth of the infant are not affected.

There are numerous theories for its histogenesis, and though none is satisfactory, the process fundamentally concerned is the saponification in situ of neutral fats in the subcutaneous tissues.

The diagnosis of this condition is not difficult and the author presents the differential points which contrast the condition from true scleroderma.

A. A. MARCHETTE.

Microscopic study of sections of the polyp revealed regions of glandular formation, manifestly carcinomatous (Fig. 2). Arrangement was atypical with occasional papillary infolding. Under the high power objective the cells were seen to be of a columnar type with large nuclei and nucleoli. The nucleonucleolar ratio of MacCarty indicated malignancy. An average of five mitotic figures was seen in each field viewed at a magnification of 500 diameters. The stroma of the polyp was made up of oval and spindle cells and an occasional giant cell was seen. The nuclei of these

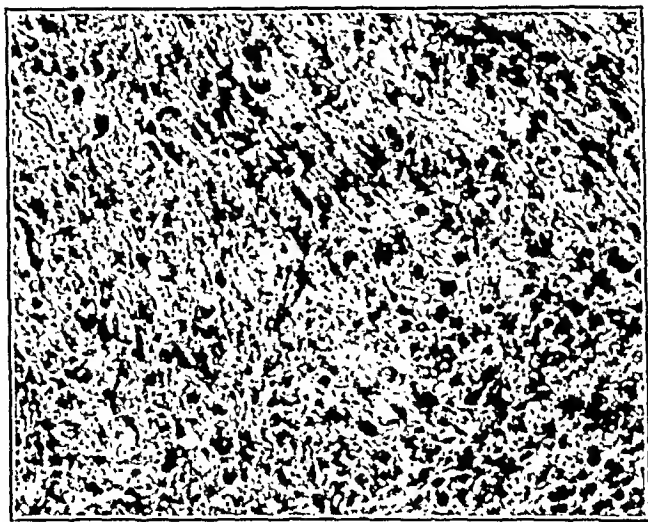


Fig. 3.—Stroma of polyp showing sarcomatous elements ( $\times 300$ ).

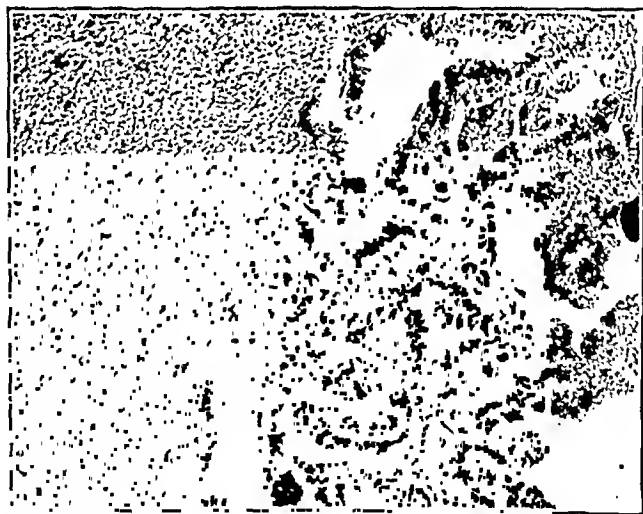


Fig. 4.—Section through polyp showing junction of sarcomatous and carcinomatous portions ( $\times 75$ ).

cells were large and dark staining. Mitotic figures were numerous; an average of 6 was seen in each field viewed with the high power objective. Vascularity was marked and the vessels were, in most instances, lined by a single layer of endothelium. No vascular invasion by tumor cells was observed in any section (Fig. 3).

In certain parts of the polyp (Fig. 4), there seemed to be a definite line of demarcation between sarcoma and carcinoma. In other parts the appearance was that of isolated carcinomatous glands dipping down into a sarcomatous stroma. The endometrium in other regions presented varying degrees of atrophy and cystic forma-

Postcoital examination (Huhner Test) revealed numerous actively motile spermatozoa one hour after coitus. Many spermatozoa also present in the cervical mucus. No abnormal forms were seen.

Biopsy of the endometrium done on twenty-sixth day of the menstrual cycle. Microscopic examination revealed large fragments of endometrial tissue, with glands elongated, widened, and tortuous. They were lined by a single layer of tall columnar cells taking the acid stain and showing secretory activity. The lining of the glands was thrown up into papillary folds. Surrounding stroma was edematous, congested, and hemorrhagic. This glandular picture was uniform in all sections on the slide. There were several foci present, composed of a central area of necrosis, a collar of lymphatic cells, and giant cells of the typical Langhans type. Ziehl-Nielsen stain failed to reveal any tubercle bacilli. Pathologic diagnosis: Physiologic hyperplasia of the endometrium corresponding to the late premenstrual phase. Tubercles suggesting tuberculosis of the endometrium (Fig. 1). The pathologic report clearly showed that ovulation had definitely occurred, but it threw a new light on the cause of the sterility by revealing the unsuspected presence of tubercles.



Fig. 1.

Are these tubercles the result of tuberculosis? It is well known that tubercles may develop in the endosalpinx following lipidol instillation. But there is no record that the endometrium is similarly affected. The periodic monthly decidualization of the uterine mucosa would hardly facilitate the formation of foreign body granulomas in the endometrium. Nevertheless, to exclude this possibility, the giant cells were searched for foreign bodies, including a polariscopic examination for doubly refractile fat. No foreign bodies were found.

To establish the diagnosis of tuberculosis beyond doubt, additional data were necessary. The family history was gone into in great detail but no instance of tuberculosis was brought to light. A Mantoux test, using old tuberculin (O.T.) was strongly positive in dilutions down to 0.000001. (The average adult may react to a dilution of 0.001 old tuberculin. A positive reaction to weaker dilutions may be interpreted as an indication of an active tuberculous infection.)

Radiographic examination of the chest (Dr. M. Friedman) on March 17, 1937, did not show any pathologic changes in the lungs. There was no evidence of a recent or old tuberculous process. The heart was approximately normal in size, shape, and position.

Another biopsy of the endometrium was done on the twenty-fifth day of the menstrual cycle. The specimen was divided into two portions, one of which was run through for microscopic examination, and the other was injected into a guinea pig. The histologic picture corresponded to that observed previously. The guinea pig was killed after six weeks, but no evidence of tuberculosis was found.

## TUBERCULOUS ENDOMETRITIS

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THE case herein reported was found accidentally to have genital tuberculosis during the course of a routine investigation of sterility.

R. E., female, white, aged 30 years, was referred on May 20, 1936, for the study of primary sterility of ten years' duration. Her previous medical, surgical, and family history was negative. Catamenia began at 14, recurring regularly every twenty-eight days for a period of three days. Eight years ago the menstrual flow diminished to that of a stain but the regularity of the cycles persisted. About that time her weight rose from 120 to 146 pounds.

Six years ago, after four years of sterility, a physician was consulted for the first time. The Rubin insufflation test revealed the tubes to be patent. The condom specimen was reported as normal. Following this investigation the patient was hospitalized, the cervical canal dilated and a stem pessary inserted. No curettage was performed. The stem pessary was removed a few months later.

Three years later she consulted another physician for the persisting sterility. A lipiodol hysterosalpingogram showed a uterus of normal size, both tubes patent to fimbriated ends. Twenty-four-hour plate showed encapsulated oil at both fimbriated ends.

In 1935 she returned because of a continuance of the sterility and hypomenorrhea. No genital pathology could be detected. Thyroid extract was prescribed and shortly afterwards the menstrual flow became heavier. Since then her cycles have been normal in every respect. The following year she was referred to me for a more complete study of the sterility.

Physical examination (May 20, 1936) revealed a well-developed and well-nourished female, height 60¼ inches, weight 146 pounds. Obesity was noted particularly about the shoulders and the trunk. Hair was brown and dry, and distributed normally except for slight excess on the legs. The skin was coarse and thickened. The thyroid was not enlarged. The pupils were equal, regular and reactive. There was no exophthalmos. The teeth were not spaced and were well preserved. The tongue exhibited marginal corrugations due to impressions of the teeth. The neck was short and thick. The breasts were somewhat pendulous, free of masses, and no secretion could be expressed from the nipples. The heart and lungs were normal. Blood pressure 124/78. The abdomen was not distended. No organs or masses were felt. The extremities were normal except for short stubby fingers. The reflexes were normal.

Vaginal examination revealed labia minora slightly hypertrophied. The clitoris was not enlarged. The introitus admitted two fingers. The vagina was roomy. The uterus was normal in size, shape, and position, freely movable and not tender. The ovaries were not enlarged. The tubes could not be palpated. A normal nulliparous cervix was seen on speculum examination.

*Clinical Laboratory Data.*—Basal metabolism (Jones) minus 10 per cent; blood Wassermann, negative; blood count: Hg was 82 per cent; red blood count, 4.5 million; white blood count, 5,400; polymorphonuclears, 48; lymphocytes, 51; monocytes, 1.

Tubal insufflation done on ninth day of the menstrual cycle; 280 c.c. of CO<sub>2</sub> gas was introduced. The pressure rose at first to 160 mm. Hg and then dropped to 80 mm. Hg, at which level the flow of gas continued without obstruction. Pain was experienced in the right upper quadrant. Fluoroscopic examination revealed an elevation of the right leaf of the diaphragm.



may even be fraught with danger for cases have been reported in which tuberculous peritonitis<sup>5</sup> or acute miliary tuberculosis<sup>6</sup> have developed after this procedure.

Some authorities advocate a "hands-off" policy. The apparent good health of the patient described above would seem to justify this attitude. Nevertheless a quiescent tuberculous focus too often becomes activated under conditions outside our control. This possibility alone warrants the radical removal of the uterus and tubes. It is to be regretted that the strong maternal instinct and the sense of well-being enjoyed by my patient have caused her to reject any treatment which would prevent conception.

#### SUMMARY

A case of sterility due to tuberculosis is described in which a tuberculous endometritis probably secondary to tuberculosis of the tubes was accidentally discovered by biopsy of the endometrium. The diagnosis was established by inoculation of a guinea pig with endometrial tissue. The patient has been under personal observation for over two and one-half years and shows no ill effects of the disease.

While conservative treatment has been followed in this case, hysterectomy and bilateral salpingectomy should be the method of choice.

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### A DEFORMED PELVIS DUE TO CLEIDOCRANIAL DYSOSTOSIS\*

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CLEIDOCRANIAL dysostosis is a rare disease, characterized by delayed or incomplete ossification of the skeleton, usually affecting most of the bones formed from membrane. We have observed a mother and her child, who had many deformities due to this dysostosis. The mother had a deformed pelvis.

Mrs. S. P., white, had had two pregnancies. The first infant was delivered by midforceps, after a second stage of labor lasting eight hours. He weighed 3,510 gm. Death occurred twenty-four hours later from an intracranial hemorrhage. Tears of the right and left tentorium cerebelli were found at autopsy. There was no evidence of cleidocranial dysostosis.

She was under our care during the second pregnancy. Her last menses began on Aug. 27, 1937. She was 25 years of age, and the youngest of eleven children. There was no history of any bone abnormalities in the family. She was told that her fontanels had been open for several years.

The permanent teeth had been extracted because they erupted late and soon became carious. One incisor had recently erupted. Her skull had a deep frontal groove and prominent frontal and parietal bosses. The nose was of the "saddle" type. Her skeletal measurements are presented in Table I. The ribs had no evidence of a rachitic rosary. The lateral half of the right clavicle and the lateral third of the left clavicle could not be palpated. The tibiae were small, but normal in contour.

The "rhomboid" of Michaelis was triangular. The pubic arch was narrow. No separation of the symphysis pubis could be felt. The posterior surface of the symphysis seemed more angular than normal. The entire linea terminalis could be

\*For lack of space, the review of the literature is included only in the author's reprints.

Slides of both biopsies were sent to Robert T. Frank who stated that "there is no question but that you are dealing with a tuberculosis of the endometrium."

*Subsequent Course.*—An attempt was made to increase the patient's resistance to the tuberculous infection by vaccination. She was given subcutaneous injections of old tuberculin twice weekly from March 22, 1937, to July 26, 1937, commencing with 0.15 c.c. of a 1:1,000,000 dilution and gradually increasing the amount until the patient could tolerate a dose of 1 c.c. of a 1:1,000 dilution. Throughout this period she exhibited no general reaction or marked local reaction to the injections. The Mantoux test was repeated in September, 1937. This time the reactions were within the normal range as she was positive to the 0.001 dilution and negative to the 0.0001 dilution of old tuberculin.

The endometrial pathology, however, remained unchanged, for another biopsy on Oct. 15, 1937, was reported by Dr. Ehrlich to exhibit lesions closely resembling the tubercles found in previous biopsies.

On June 7, 1938, the patient was admitted to Lebanon Hospital for a thorough curettement. Her physical status was no different than when examined a year previously. Under anesthesia the uterus and adnexa were carefully palpated, but no distortion or enlargement could be felt. The endometrium was removed by sharp curette. The specimen was divided into two portions, one for routine microscopic examination and the other for guinea pig inoculation. The pathologic report again revealed typical tuberculous granulomas. The guinea pig was autopsied after six weeks, and this time tuberculous foci were found in the diaphragm, liver, and spleen.

The diagnosis of tuberculous endometritis was now definitely established.

The patient was last seen Feb. 15, 1939, still complaining of sterility. She is in apparent good health and exhibits none of the clinical features of an active tuberculous lesion such as weight loss, increased pulse rate, and rise in afternoon temperature. Her menses are regular and normal in character. The vaginal discharge is scanty.

#### DISCUSSION

Primary tuberculosis of the endometrium is a most unusual entity. Gordeler<sup>1</sup> (quoted by Norris) in 1913 found 1 case in 4,620 post-mortem examinations in a hospital for tuberculous patients. Norris<sup>1</sup> never saw a case of proved tuberculous endometritis in which the tubes were not involved. On the other hand, Siddall<sup>2</sup> recently reported a case accidentally discovered by curettage in which the lesion was found to be limited to the endometrium when hysterectomy and bilateral salpingectomy were performed.

In view of the rarity of primary tuberculous endometritis and for want of more complete histologic studies of the uterus and tubes, it is quite likely that the patient here reported has a coexisting microscopic tuberculous lesion in the tubes. The persisting sterility also favors this assumption. It is doubtful whether the scattered tubercles seen in the secretory endometrium could prevent nidation once impregnation occurred, but fertilization of the ovum could be inhibited by a tuberculous endosalpingitis.

The treatment of choice for tuberculosis of the uterus is hysterectomy and bilateral salpingectomy. It offers the best prognosis particularly when the disease process is limited to the uterus and tubes. Jameson,<sup>3</sup> in an excellent review of genital tuberculosis, states that most authorities prefer radical surgery even in the presence of more extensive pathology.

X-ray irradiation has also been tried, but it is most effective in the treatment of sinuses which may develop following operation. Mensing<sup>4</sup> reported a case of a patient with tuberculous endometritis who was treated with 1200 mc.hr. of radium, but he failed to prove whether a cure occurred by performing a subsequent curettage for further histologic study of the endometrium.

Curettage alone cannot be expected to cure primary tuberculosis of the endometrium, because the disease usually involves the myometrium as well. It is still less effective in the treatment of secondary tuberculous endometritis. It

## PURPURA RHEUMATICA COMPLICATING THE PUERPERIUM

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UP UNTIL July, 1937, there have been approximately eighty cases of purpura hemorrhagica complicating pregnancy and the puerperium reported in the literature. Of all these cases only one, which was reported by Barnes in 1867, showed rheumatic symptoms, and in this case they were rather indefinite.

Mrs. E. B., aged 22 years, white, gravida ii, para i, Kahn-negative, was admitted to the ante-partum clinic May 25, 1938. Last menstrual period was Dec. 4, 1937, and expected date of confinement was Sept. 11, 1938. The family history was essentially negative.

The patient had had the usual childhood diseases, no diphtheria, scarlet fever, or other serious illness. Appendectomy several years previously. She denied venereal infections.

She was delivered in 1937 of a full-term infant. At this time she had a mild toxemia, secondary anemia, and a possible attack of malaria fever.

Menstrual history was perfectly normal, beginning at the age of 13 years, regular every twenty-eight days, of five days' duration, and the flow had always been normal.

When seen in the clinic, the patient's physical examination was normal, except for slight decay of the teeth and a systolic murmur over the apex. At this time she was approximately five months pregnant, and showed a red cell count of 2,312,000 and hemoglobin of 8 gm. per 100 c.c. of blood. Iron at this time was given for the anemia. During her ante-partum period her blood pressure varied from 110/70 to 120/95, and she showed a net gain of 7.5 pounds. Early in August she complained of pain and swelling in her left ankle, for which she was given salicylates and hot foot baths, which gave her relief. Otherwise her ante-partum course was perfectly normal.

On Sept. 30, 1938, the patient was admitted to John Gaston Hospital in the first stage of labor. On admission she was at full term and the cervix was beginning to dilate. Her blood count at this time showed 3,100,000 red cells, hemoglobin 10 gm., and 8,800 white cells. The differential count was normal and the urine was negative. After a slightly prolonged labor of twenty-five hours and fifty minutes, she delivered a living normal full-term infant spontaneously. The bleeding at the time of delivery was very slight. Her puerperium was normal until the third day of October when her temperature suddenly rose to 101.6° F. and her pulse to 136. At this time maculopapular purpuric spots, which varied from 1 mm. to 3 cm. appeared suddenly over her shoulders, buttocks, legs, torso, plantar and dorsal surfaces of the feet, face, and even on her scalp. These spots were purple in color, slightly tender, and did not disappear on pressure. The lochia at this time were normal and the blood pressure 118/70. On October 4, these areas had increased in size and some of them had coalesced. The left ankle was swollen, red, and very tender to movement and pressure. Over the metacarpals of the right hand was an area of edema, redness and tenderness. Both shoulders and right ankle were extremely tender and painful to both passive and active motion. There was a blowing systolic murmur over the valvular areas, transmitted to the vessels of the neck. The spleen was enlarged to 4 cm. below the left costal margin, and the liver was about 1.5 cm. below the right costal margin. The uterus was firm, and three fingers below the umbilicus. The blood count at this time had dropped to 1,450,000 red cells, hemoglobin 7 gm., 2,250 white cells,

palpated. It extended straight backward on each side with slight concavity. The ischial spines were "hooked." The sacrum was flat from side to side, and the promontory seemed to "overhang" the inlet.

Her blood calcium was 9.4 mg. per 100 c.c.; blood Wassermann test was negative. A slight hypochromic anemia was present.

A living male child, weighing 4150 gm., was delivered on May 23, 1938, by a low cervical two-flap cesarean section. We measured the transverse diameter of the pelvis with a DeLee pelvimeter (Table II) during the operation, but we were unable to measure the conjugata vera accurately, due to a "false promontory" of the sacrum.

Both clavicles of the infant were abnormal. The right clavicle was about 1 cm. in length, and the outer two-thirds was absent. The left clavicle was slightly longer. The sagittal and frontal sutures were wide open, but there was no bulging of the fontanel. The frontal and parietal bosses were prominent. Anyone unfamiliar with this disease might, at first glance, make a diagnosis of hydrocephalus. In other respects the infant appeared normal.

The pelvis of our patient was reduced in all of its dimensions except the antero-posterior diameter of the outlet (Table II). The inlet was "heart shaped"; the posterior surface of the pubis was angular; and the subpubic angle was acute. It closely resembled that of a generally equally contracted rachitic pelvis.

TABLE I. SKELETON MEASUREMENTS

Weight	35.7 kilos
Height	137.0 cm.
Circumference of skull	22.4 cm.
Humerus	26.0 cm.
Ulna	21.0 cm.
Femur	39.5 cm.
Tibia	33.0 cm.
Xiphoid to symphysis	28.0 cm.

TABLE II. PELVIC MEASUREMENTS

Interspinal	21.0 cm.
Intercristal	22.5 cm.
External conjugate	18.0 cm.
Diagonal conjugate	10.0 cm.
Transverse of outlet	7.5 cm.
Anteroposterior of outlet	12.0 cm.
Posterior sagittal	8.25 cm.
Transverse of inlet*	10.50 cm.
True conjugate*	9.25 cm.
Transverse of inlet†	10.00 cm.

\*By roentgenogram.

†At operation.

## COMMENT

Possibly the second infant of our patient could have been delivered through the pelvis, but in view of her previous difficult labor, we felt that delivery by a hysterotomy was indicated. The infant's weight (4150 gm.) was greater than any yet reported in the literature on this subject. Also our patient was shorter (137 cm.) than the patients reported as being delivered without difficulty.

The type of pelvis found in women with cleidocranial dysostosis is still a matter open for further study. More patients must be examined by the Thoms method or by the stereoscopic method of Caldwell and Moley, before one can definitely answer this question.

The baby was perfectly normal and well. There were no signs of any purpura and the weight curve was practically normal.

The patient returned for a post-partum check-up examination on Nov. 12, 1938. At this time all of the lesions were completely healed, but showed some scarring, particularly around the hips. There had been no new lesions. The spleen was still large and the liver was palpable about 1 cm. below the right costal margin. The pelvic organs were normal, and there was a moderate amount of mucopurulent leucorrhea. The blood count showed 3,400,000 red cells, 8.8 gm. of hemoglobin, 5,200 white cells, and 180,000 platelets. The tourniquet test was normal and her general condition was good. The baby was tested for any signs of hereditary purpura and showed both a normal blood picture, and normal bleeding and coagulation times.

The etiologic factors in this case were thought to be a vitamin and a calcium deficiency during the ante-partum period associated with a mild toxemia of pregnancy.

The authors wish to express their appreciation to Dr. J. L. Scianni for the illustrations, and the cooperation of the attending, house, and nursing staffs of the Maternity Pavilion of the John Gaston Hospital for their cooperation in this case.

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## MONOAMNIOTIC TWIN PREGNANCY WITH LIVING INFANTS

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THE following case is reported because of the relative rarity of twins developing in one amniotic sac and because of the greater infrequency of survival of both infants. Monoamniotic twins occur once in approximately 10,000 pregnancies. Quigley, in 1935, reported the only case in the American literature in which even one infant of a monoamniotic twin pregnancy survived. In his comprehensive review of the 109 cases previously reported, both twins had lived in only 17 instances. He found the fetal death rate of monoamniotic twins to be 68 per cent. Since Quigley's presentation, two additional cases have been reported in the United States. In neither case did both twins live.

As far as we have been able to determine, the following case is the first in the American literature in which both infants of a monoamniotic twin pregnancy have survived.

D. G., colored primipara, aged 17 years, was admitted to Gallinger Municipal Hospital on April 12, 1939, with ankle edema of three weeks' duration, blurring of vision for three days, occasional abdominal cramps, and a blood pressure elevation of 150/120. Her last normal menstrual period began Aug. 15, 1938, making the expected date of confinement May 22, 1939. Quickening occurred in December, 1938. Family history was of interest in that the patient's maternal grandmother had twin boys who were reported as identical in appearance. The patient's husband's great-grandmother gave birth to twin girls who were said to be identical.

The patient was a well-developed, well-nourished, rational, young colored woman near term, and not in labor. Eye grounds showed some arteriospasm. Blood pressure was 150/120. Abdomen showed a fairly tense ovoid tumor of a pregnancy at or near term. Fetal head was in the left upper quadrant of the abdomen. Small parts were palpable on the right. Fetal heart sounds of approximately the same rate, 150 to 160 per minute, were heard in the left upper and left lower quadrants of the abdomen. Multiple small parts suggested twins, but a confirmatory x-ray plate was not obtained. Pelvic measurements were within normal limits. Extremities showed two plus edema.

and the platelet count was found to be 43,500. The differential count showed 82 polymorphonuclear leucocytes, large lymphocytes 6 per cent, small lymphocytes 12 per cent. No malarial organisms were found, coagulation time was one minute, and the bleeding time two and one-half minutes. Blood calcium 8.5 mg. per 100 c.c. of serum, and the blood culture was negative. The urine at this time was negative except for an occasional red blood cell.

The hemorrhagic areas continued to increase in size and number, especially around the joints. In the areas which came in contact with the bed, the hemorrhagic spots became confluent, assumed a bleb-like appearance from which exuded a bloody serum, and these areas were surrounded by a zone of erythema. These areas were not tender to pressure, but did itch and the soles of the feet had a burning sensation. The mucous membranes at no time showed any involvement, and the lochia did not increase in amount.

Immediately upon the appearance of the purpuric areas the patient was given a blood transfusion of 500 c.c., 5 c.c. of calcium gluconate twice a day hypodermically, 5 c.c. of hemostatic serum intramuscularly every four hours, and vitamins were given in the form of yeast and a high vitamin diet. The purpuric areas continued to enlarge, and the patient was given another transfusion of 500



Fig. 1.—Showing patient at the onset of the attack of purpura rheumatica.

c.c. of whole blood the day after the appearance of her symptoms. On October 6 and 7, her spleen was irradiated. Following this treatment the bleeding time increased to three minutes and the blood count showed 2,200,000 red cells, 8.1 gm. of hemoglobin, and 11,200 white cells. The platelet count also increased to 150,000.

It was suggested at this time that the purpura was due to an allergic condition of unknown origin. Therefore, the patient was given some of each drug that she had taken previously, without any flare-up of her condition. Due to information obtained from the husband, the etiologic factor was determined as due to a low calcium and vitamin diet during the ante-partum period, along with the possibility of toxemia.

Under the treatment as outlined above, the edema and the tenderness of the joints disappeared and no new spots appeared. The old purpuric lesions gradually dried up, and became covered with a black purplish crust. The temperature continued to run a slight septic course between 99° and 100.6° F. The pulse returned to 90, and remained approximately at that rate. The patient was given another transfusion of 750 c.c. of whole blood one week after the appearance of the purpura. The platelet count rose to 159,500 and remained comparatively stationary. The red count increased to 3,860,000 with 9 gm. of hemoglobin. The general condition of the patient continued to improve, and on October 16, she was discharged from the hospital.

pressure was 140/100. On the eleventh day after delivery, the patient was discharged from the hospital with no edema, a well-involuted uterus, and a blood pressure of 125/85. Both infants received breast milk. When discharged with the mother, infant A weighed 5 pounds 5 ounces (2,410 gm.). Infant B developed a mild upper respiratory infection and failed to gain weight very rapidly. On the thirty-first day after delivery, infant B was discharged from the hospital weighing 5 pounds 6 ounces (2,438 gm.). Except for prematurity, both infants were normally developed. X-ray plates of the infants' chests failed to reveal any abnormality. The finger and foot print patterns of the two infants were entirely different.

Six weeks after delivery, the patient's blood pressure was 128/78 and her pelvic organs were normal. Both infants had gained in weight and appeared healthy.

1843 BURKE STREET, S. E.

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## PNEUMOCOCCUS, TYPE III, ASSOCIATED WITH PELVIC INFLAMMATORY DISEASE

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A WOMAN with pneumococcus pelvic inflammatory disease was recently observed at Mercy Hospital, and the record of another patient was found in the archives of the University Hospitals. A description of the clinical courses of these two patients seems justified, since Nuckols and Hertig<sup>1</sup> reviewing the reported cases in May, 1938, were able to discover but 77 instances of pneumococcus genital tract infection in women. Of these 77 patients, the infection followed the delivery of a term or near-term baby in 34, was associated with abortion in 17, and was unassociated with any history of a recent obstetric episode in 23. The remaining 3 women, strictly speaking, did not have genital tract infection, but developed pneumococcus peritonitis during pregnancy.

CASE 1.—Mrs. J. W. K., aged 39 years (Hospital No. 1620), was admitted to Mercy Hospital late in the evening of Sept. 17, 1938, complaining of severe abdominal cramps which began twenty-four hours previously. Following onset, the pain gradually became intensified and was accompanied by a diarrhea which developed into a profuse watery discharge. The leucocyte count shortly after onset was 22,000 cells per cubic millimeter. The subcutaneous injection of 0.25 gr. of morphine sulphate relieved the symptoms and the patient became reasonably comfortable until afternoon of the day of admission, at which time a constant abdominal pain accompanied with nausea, but not vomiting, appeared. Two hours before admission the patient suffered a severe, bed-shaking chill. Following the chill, the abdomen became diffusely tender, the lower abdominal cramps became intensified, and the patient passed two watery stools. The catamenia began the day before onset of the present illness. As a young girl, the patient was severely ill with pneumonia, but otherwise had experienced no more than an average amount of illness. One year before admission she suffered from a transient illness characterized by lower abdominal pain and cramps, but recovered after routine treatment for colitis. The last of a series of 4 pregnancies occurred six years ago.

On admission, the patient was acutely ill, with the mouth temperature ranging between 100° and 103° F., the pulse between 80 and 120 beats per minute. On physical examination the nose and throat were normal and the lungs were clear. There was generalized abdominal tenderness with moderate rigidity and no distention. There was no evidence of genital gonorrhea, and cultures from the cervix and

*Laboratory Findings.*—Kahn was negative. Urine showed 5.5 gm. per liter of albumin (Esbach). Blood studies showed hemoglobin 54 per cent, red blood count 3,300,000, white blood count 8,500, urea nitrogen 10 mg. per 100 c.c. blood, sodium chloride 460 mg., and cholesterol 240 mg. per 100 c.c. blood.

With bed rest, sedation, and a salt-free diet, patient showed no improvement in her pre-eclamptic symptoms. On the third day following admission, labor was induced with a hot enema, and a total of six minims of pitocin were given in divided doses. The fetal head was engaged. The membranes ruptured spontaneously half an hour before the onset of active labor. The first stage of labor lasted two hours and thirty-five minutes.

The second stage of labor became complicated by infrequent, weak contractions with the fetal head low in the pelvis in L.O.P. position. Fetal heart sounds, heard at a level with the umbilicus on the left, became too rapid to count. Following a left mediolateral episiotomy, a living, premature, female infant (A) weighing 4 pounds 13¼ ounces (2,187 gm.) was delivered with low forceps. Normal fetal respiration was established within a few minutes following the administration of oxygen to the

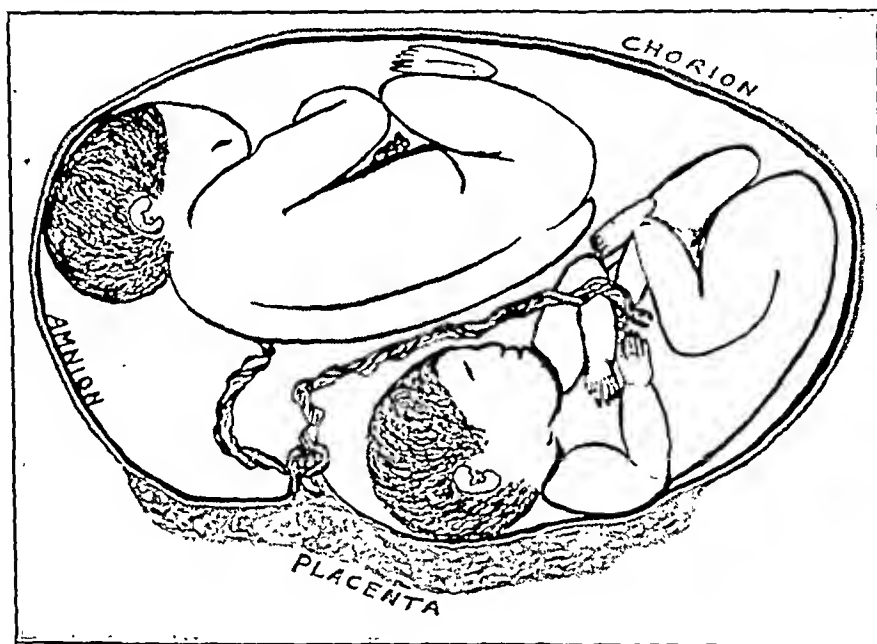


Fig. 1.

infant. Immediately following delivery of the first infant, the left hand of the second baby prolapsed into the vagina. The second infant (B) was found to be presenting in left acromiiodorsoposterior position. Immediate podalic version and extraction of a living, premature, female infant, weighing 4 pounds 8¼ ounces (2,047 gm.) was performed. The second infant breathed and cried spontaneously. Duration of the second stage of labor was one hour and forty-five minutes.

The placenta separated spontaneously and was expressed from the vagina thirty-six minutes after the birth of the second infant. Placenta weighed 885 gm. and measured 20 by 16½ by 3 cm. Cord to infant A measured 48 cm.; cord to infant B was 58½ cm. long. Nine centimeters from their placental insertions, the cords formed a true knot. There were anastomoses of the placental vessels going to the cords. Careful examination failed to reveal any evidence suggestive of an amniotic septum between the cords. The maternal surface of the placenta was uniform with normal cotyledons.

The mother's hospital course was afebrile. By the fifth post-partum day, edema had completely subsided, urine showed only a trace of albumin, and the blood



associate this with the present illness. Despite the cough this was presumably an ascending genital tract infection, since physical, roentgenographic and fluoroscopic examinations of the chest were negative.

CASE 2.—Mrs. L. B., aged 20 years (Hospital No. D-9285), was delivered of a 3,470 gm. baby on the Obstetric Service of the University Hospitals, Dec. 31, 1929. The labor was spontaneous, the puerperal course was uneventful except for a fever on the sixth day, and the patient was in good condition with normal pelvic viscera at the time of discharge on the sixteenth post-partum day. A gradually increasing, constant, right lower quadrant pain began about two weeks after discharge, to be followed one week later by daily, afternoon attacks of sharp, severe pains in the same region. There was some burning and smarting on urination, but the patient was uncertain as to the presence of fever, although she admitted that she perspired a great deal at night.

On re-admission, Feb. 18, 1930, the patient obviously was ill. There was no evidence of pulmonary or upper respiratory tract disease. The cervix was closed and the uterus was displaced toward the left by an orange-sized mass. There was tenderness and induration in the left adnexal region. During the hospital course, the temperature ranged from 99.0 to 102.0° F. and the pulse from 90 to 110 beats per minute. Weakness and listlessness were marked. The white cell count, which was 14,900 per c.mm. on admission, gradually rose during three weeks to 26,000. The patient was treated with heat and foreign protein, and twenty-one days after re-admission the right adnexal mass was drained through the vaginal fornix of about 250 c.c. of greenish pus. Pneumococcus, Type III, was cultured from the pus. On the day following operation, there was very little drainage from the abscess, the pulse rate rose to 140 to 150 beats per minute, and it was obvious that the patient had a spreading, generalized peritonitis. The blood was cultured at this time and a Type III pneumococcus was recovered. She died March 16, 1930, five days after operation and twenty-seven days after re-admission. Post-mortem examination of the abdomen revealed a generalized peritonitis, and pneumococcus, Type III, was cultured from the peritoneal exudate. Although the chest was not examined post mortem, it is doubtful if the patient had any lung involvement, since there were no pulmonary symptoms or signs during the clinical course.

Although this patient experienced comparatively good health for the month following labor, the genesis of the infection presumably dates from that time. She should, therefore, be added to that group of 34 recorded cases which followed pregnancy. In all probability this was also an ascending genital tract infection, since there was neither history, symptom, nor sign of any antecedent infection of consequence.

#### DISCUSSION

Nuckols and Hertig<sup>1</sup> and others, insist that the idea of ascending origin of pneumococcus genital tract infection cannot be accepted in any case unless there has been a careful elimination by clinical, pathologic, and bacteriologic means of all other possible sources. Tompkins,<sup>2</sup> however, says, "Generally speaking, unless there is a clear history to the contrary, obstetricians and gynecologists will not be far wrong in assuming that cases of pneumococcus pelvic disease which they see are the result of ascending infections."

The true nature of the infection was not suspected in either patient until bacteriologic examination of pus was possible, and it is difficult to understand how it could have been otherwise. King<sup>3</sup> emphasizes that the clinical signs of pneumococcus genital tract infection are no different from those caused by other organisms. It should be noted, however, that each of the two patients here reported had the extreme prostration and rapid localization of pus, characteristic, although not diagnostic, of pneumococcus infections.

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vaginal vault did not contain the diplococcus. The cervix was closed and lateral motion was painful. The uterus seemed to be in midposition and was thought to be slightly enlarged. There was tenderness and induration in each adnexal region, making adequate definition of the ovaries impossible. The hemoglobin was 92 per cent, and there were 38,450 white blood cells per c.mm.

Despite failure to demonstrate the gonococcus, and despite the fact that the patient was prostrated out of proportion to the extent of the clinical and laboratory findings, a provisional diagnosis of acute pelvic inflammatory disease was made.

For the next twelve days, the illness was characterized by pain in the abdomen, headache, severe nausea and vomiting, marked abdominal distention and frequent watery stools, numbering 10 on one day. The leucocyte count fluctuated between 6,700 and 20,900 cells per c.mm. Pus localized in the cul-de-sac, and there was a suggestion of localization in the right adnexal region. On the fourteenth day of the illness, 200 to 300 c.c. of yellowish green pus were drained from the cul-de-sac following puncture, and pneumococcus, Type III, was identified by the usual technique. Despite the drainage, the general condition did not improve, and the patient gradually became worse. She complained bitterly of headache, pain in the abdomen, and was nauseated and vomited frequently. The number of daily liquid stools, however, decreased sharply. On the twenty-sixth day of the illness, the right adnexal abscess was drained through the vaginal fornix of about 200 c.c. of pus. Gradual general improvement followed the second drainage, until the thirty-second day when there was an elevation of temperature and pulse rate. Two days later the pelvis was examined under anesthesia, the draining sinuses were reopened, but no additional pus was found. The general improvement which had been temporarily halted was soon resumed, and on the fiftieth day the fever abated. She was dismissed from the hospital on November 16, the sixty-first day of the illness.

During the first half of the hospital stay, the patient received one and, in several instances, two or three daily intravenous injections of saline and glucose solutions. Supportive measures included sulfanilamide during the early days of the illness, repeated small blood transfusions, vitamin "B," and pelvic diathermy after the acuteness of the condition had subsided. Pneumococcus, Type III, antiserum was not used, since it is generally recognized that, to be effective, it must be administered early. At this time the patient complained of pain in the right and later in the left chest, and on one occasion the lower portion of the chest was strapped with adhesive tape in order to relieve this pain. However, no physical evidence was ever found, indicating involvement of the lungs. Also, there was never any cultural evidence of a pneumococcal septicemia. There was, however, a dry nonproductive cough suggestive of pleural irritation. This cough persisted for a few days, even after discharge, and may have resulted from a common cold.

Two days after discharge the patient was re-admitted, complaining of left-sided abdominal pain and tenderness, and pain in the right chest. A roentgenogram and fluoroscopic examination of the chest revealed no evidence of pulmonary disease and physical examination was entirely negative. There was, however, a recrudescence of fever which persisted for thirteen days and reached a height of 102.2° F. Following eighteen days of normal temperature and pulse rate she was again discharged, after a combined hospital stay of ninety days. She has remained well since, and was examined a month and a half after final discharge from the hospital. At this time the pelvic organs were so completely normal, that no traces of the inflammation could be found. The uterus was normal in size and freely movable, the adnexa were normal, and there was not the slightest evidence of residual induration. The lungs were clear and there was no apparent damage to the heart, which was normal in size and action. Subjectively, the patient had not completely regained her strength, although she was able to carry on average activity.

This patient must be classified with the "localized abscesses" of which Nuekols and Hertig<sup>1</sup> were able to collect 23 examples. It is of interest to note that there was no antecedent history of illness and that the last pregnancy occurred six years ago. There is a history of pneumonia in childhood, but it does not seem logical to

to be an imperforate hymen. The last operation was performed at Grady Hospital under a diagnosis of imperforate hymen and hematometrium. Operation disclosed absence of the vagina, and no cervix could be found after exploring the rectovesical space for two inches. Laparotomy then revealed a rudimentary right ovary and cornu and no left adnexa. The supposed hematometrium proved to be a fused pelvic kidney. No attempt was made to line the rectovaginal space with epithelium, and it was allowed to heal. A depression 1 cm. in depth was left in the site of the supposed hymen.

To overcome any difficulty of intelligent cooperation, a device was made which the patient could wear at night and which would exert constant, uniform pressure. This consisted of a short hard glass test tube 2 cm. in diameter with a rubber stopper. It was held in place by means of elastic bands attached to a closed cup-hook in the stopper and to a belt of adhesive tape around the waist (Fig. 1).

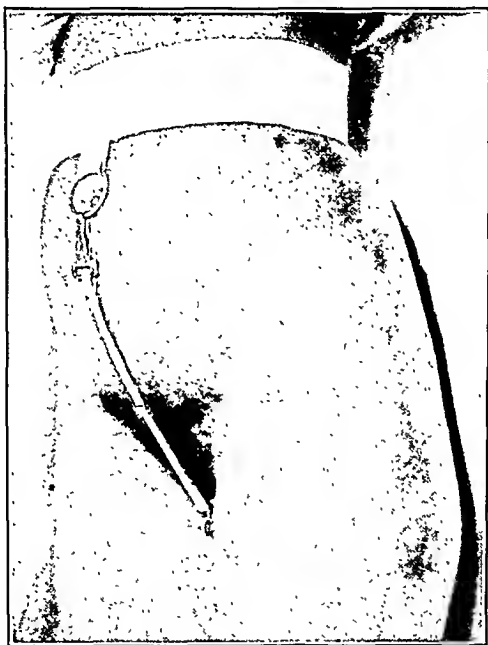


Fig. 1.

The patient was instructed to discontinue the use of the apparatus if any blood, denoting injury to the mucosa, should be found. In addition, for lubrication of the tube, she was given a solution of estrogenic substance in oil to stimulate growth of the epithelium. The test tube was replaced with a longer one as required.

The procedure was rapidly successful, no scarring from the previous operations being met with. At the end of eight weeks a vagina was secured which was 6.5 cm. deep, admitted two fingers, and accommodated a completely opened Graves' virgin speculum for its entire length. The epithelium was intact and was somewhat rugose as in the normal vagina. A pinch biopsy from the depth of this newly made vagina revealed the normal stratified squamous epithelium, typical of the adult vagina.

The patient states that intercourse is perfectly satisfactory to both parties.

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# THE FORMATION OF AN ARTIFICIAL VAGINA WITHOUT OPERATION BY THE FRANK METHOD

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CONGENITAL absence of the vagina is a not infrequent malformation for the correction of which various operative procedures have been devised. In general the methods used are highly technical and require complicated stages of plastic surgery and long periods of hospitalization. Recently Robert T. Frank<sup>1</sup> reported the successful formation of an artificial vagina by a simple nonoperative technique. The principle involved in his method is the production of a hernia of the vestibular mucous membrane into the loose areolar space that lies between the rectum and bladder. The pouch thus formed is of sufficient dimensions and elasticity for coitus and is lined with stratified squamous epithelium almost identical with that of the normal vagina. The method is an office and home procedure without danger, and the end result is free from such esthetic objections as annoying discharges, mutilation of the labia, scarring of the thighs, etc.

We wish to report two cases of successful formation of artificial vagina by the Frank procedure, one of which represents an extension of the method to a patient on whom previous operative procedures had been performed.

CASE 1.—An unmarried white woman, aged 21 years, was admitted to Emory University Hospital July 18, 1938, with the history of never having menstruated. She was told by her family physician that she could not be a "full grown woman" until she had an operation, because she did not have a vagina.

The patient was a well-nourished and well-developed young woman, with essentially feminine secondary sex characteristics. General physical examination was negative except for the pelvis. On exposing the vestibule there was an apparent absence of the vagina. The vaginal orifice was represented by a shallow depression about 1 cm. in depth. Rectal examination revealed a small indefinite cordlike structure in the region normally occupied by the uterus. A small ovary was palpable on the left side; the right ovary was not palpable.

The patient cooperated readily in carrying out the Frank method of treatment. A small glass tube 0.8 cm. in outside diameter was introduced in the center of the slight depression in the hymenal region, and gentle pressure was exerted in a direction backward and inward with the patient in the lithotomy position. She was taught to perform this maneuver and instructed to repeat it three times daily for a period of about a half hour at a time. As the depression increased in depth a longer tube 1.5 cm. in diameter, and finally one 2 cm. in diameter were used.

It was found unnecessary to keep the tube in place during the night with cotton pads and T-binder as advised by Frank. After a period of four months, an artificial vagina was formed which measured 6 cm. in depth, readily admitted two fingers, or a small bivalve Graves' speculum. The canal was lined with soft velvety mucous membrane, sections of which showed it to be normal squamous epithelium. This patient is engaged and expects to be married soon.

CASE 2.—At the Gray Clinic of Grady Hospital, a colored girl of 17 years offered herself for treatment because of absence of the vagina. There was some doubt of the applicability of Frank's method because of the limited intelligence of the patient and because two operative procedures had been performed upon her. The first of these was apparently mere incision into what was thought

atrophic. The right ovary was replaced by a hemorrhagic tumor that was 8 cm. in diameter. Much of the tumor appeared to be cystic but many solid portions were present. These latter, when freed from blood clots, were composed of a firm, granular substance, grayish brown in color, and resembling liver sausage in consistency. Rupture had occurred and much of the tumor was fragmented. However, careful study revealed the presence of a comparatively smooth capsule. Microscopically, the tumor was a typical, granulosa cell neoplasm of the mixed cylindroid and sarcomatoid patterns (Fig. 1). Vascularity was an outstanding feature. Mitotic figures were few in number and as in most examples of this type of neoplasm were suggestive of a low grade of malignancy.

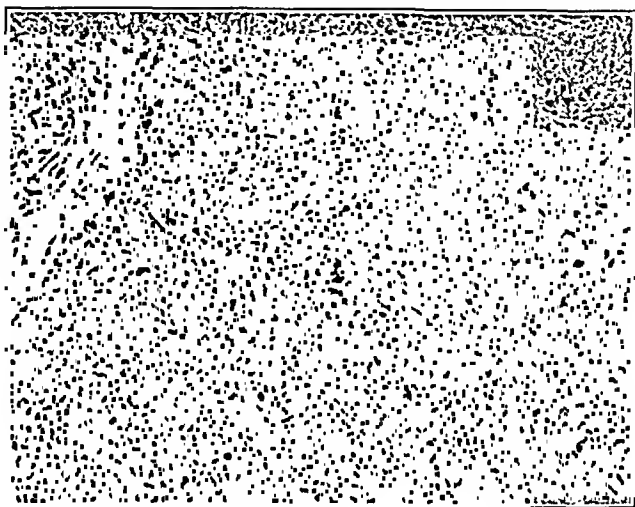


Fig. 1.—Tumor showing the cylindroid pattern of a granulosa cell neoplasm.  $\times 100$ .

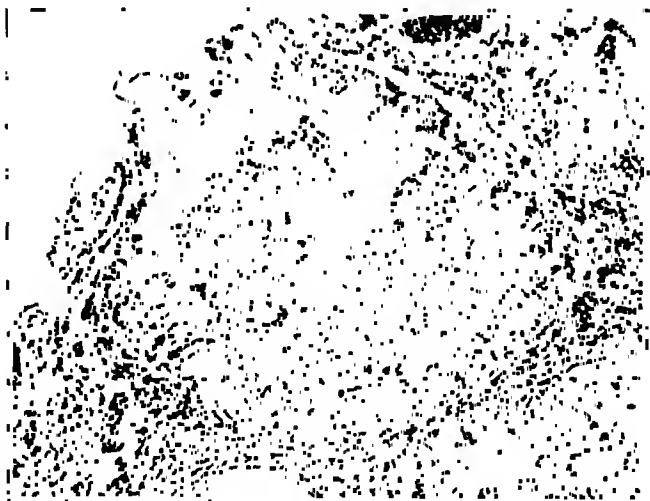


Fig. 2.—Early adenocarcinoma of the uterus associated with a granulosa cell neoplasm.

The endometrium was cystic, reflecting the prolonged action of estrin. Here and there were regions of atypical glandular epithelium forming an adenocarcinoma, Grade 1, in situ (Fig. 2). This latter change was not observed in the tissue removed in 1927 (Fig. 3) which showed the usual picture found in cases of granulosa cell neoplasm.

# A GRANULOSA CELL TUMOR OF THE OVARY WITH OBSERVATIONS ON RADIOSENSITIVITY\*

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IN RECENT gynecologic writings,<sup>1</sup> the subject of granulosa cell tumors of the ovary has received considerable attention. This "newcomer" has been studied clinically, pathologically, and biologically by a number of investigators whose contributions have added to the subject of gynecologic pathology a chapter of lasting interest. Recently, Butterworth<sup>2</sup> submitted valuable histogenic data by his demonstration that tumors, histologically and biologically composed of granulosa cells, could be produced experimentally in mice, by the use of roentgen rays. But the question of radiosensitivity in granulosa cell neoplasms has never been answered satisfactorily. These tumors are comparatively rare and hence, as pointed out by Wolfe and Kaminester,<sup>3</sup> the opportunity for studying their response to radiation is very unusual. For this reason, we believe that the following illustrative report of a case might serve a well-intended purpose.

## REPORT OF A CASE

A white woman, aged 49 years, first registered at the Mayo Clinic Nov. 16, 1917, complaining of dizziness. Her family history and personal history were irrelevant. She had had one child in 1897 and two miscarriages shortly thereafter. Menses always had been regular but the flow was becoming scanty. Examination led to a diagnosis of chronic cholecystitis and a menopausal neurosis for both of which conditions a medical regimen was outlined.

On her second admission in September, 1927, at the age of 59 years, the patient stated that, after her apparent menopause in 1924, periods had returned. The bleeding which had occurred with comparative regularity was interrupted by periods of amenorrhea during summer months. Positive physical findings at this time were an enlarged uterus, thought to contain small fibroid tumors.

On Oct. 19, 1927, dilatation and curettage were done with the insertion of radium (1200 mg. hours) designed to hasten the onset of a complete menopause. The pathologic report on the tissue removed was "hypertrophic endometrium."

On her third visit in June, 1930, the patient stated that vaginal bleeding had not occurred from October, 1927, to January, 1930. Since that time, however, there had been irregular spotting with the passage of occasional clots. Two days prior to admission the patient had been seized with severe lower abdominal pain of a cramping nature. The pain had persisted in spite of the administration of morphine. Examination revealed lower abdominal tenderness with rigidity. The uterus was difficult to outline but was enlarged, firm, and tender.

Laparotomy was performed and a hysterectomy with bilateral salpingo-oophorectomy was done because of a hemorrhagic ovarian neoplasm that showed evidence of recent rupture.

The patient was dismissed from the hospital after a satisfactory convalescence. In a follow-up letter, dated July 6, 1937, she reported that "the operation was successful."

*Pathologic Examination.*—Grossly, the uterus was enlarged in all its dimensions and presented a thick, boggy endometrium which belied the age of the patient. The Fallopian tubes were not remarkable. The left ovary was fibrocystic and

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## CARCINOMATOUS TERATOMA (TERATOBLASTOMA) IN A GIRL OF EIGHTEEN\*

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THE following case report is presented as an example of this rare condition: H. S., female, aged 16 years, was first seen in March, 1936. She had been under observation for the preceding nine months for recurrent attacks of nausea, vomiting, and abdominal pain. These attacks occurred at irregular intervals, particularly after physical exertion. During this period she also had noticed gradual enlargement of the abdomen. There was an increase in body weight from 128 to 147 pounds.

The diagnosis of gravidity was entertained by her physician, in spite of her repeated assertions that menstruation was always regular and normal. Several Friedmann tests for pregnancy were negative. A diagnosis of ovarian cyst was then made, for treatment of which she was referred to one of us (I. S.).

When seen on March 19, 1936, she was a fairly well-nourished girl, quite apprehensive, somewhat paler than normal but, to all appearances, in good condition. Physical examination was essentially negative. Inspection and palpation showed a large, ovoid intraabdominal tumor, reaching from the symphysis to a level midway between the umbilicus and the diaphragm. The shape and contour of this tumor resembled in every respect a gravid uterus of about seven and one-half months' gestation. The abdominal wall was tense and somewhat tender. The tumor was easily outlined. It was freely movable, cystic in character, and a distinct fluid wave was ascertained. Vaginal examination showed an intact hymen. Rectally, a small cervix was felt high in the pelvis, and the lower pole of the tumor was easily palpable. The diagnosis of a large ovarian cyst was corroborated and operation advised.

*Clinical Course.*—She disappeared until April, 1938, two years later, at which time she was again referred for consultation by another physician with the following interval history:

Before consenting to an operation, she entered another hospital where she was carefully studied. The diagnosis of ovarian cyst was also made, operation likewise advised and the patient again demurred. Her physician wrote: "Operation had finally been decided upon when she suddenly felt her abdomen become flat again. She experienced no pain, but found that the tumor had suddenly disappeared. Examination at this time (June, 1937) showed the abdomen to be entirely flat with no suspicion of any growth, at least to an extent that might be felt externally. I concluded that she had had a cyst which had ruptured, and advised against operation at this time. No rectal examination was made."

She was again examined by her physician in November, 1937, at which time she was apparently perfectly normal, asymptomatic, and without abdominal enlargement. Rectal examination was not made. In April, 1938, she returned with recurrence of her original symptom. She was advised to enter the Bronx Hospital, which she did on April 16, 1938, and the following was noted:

*Hospital Admission (No. 87739).*—A young, fairly well-developed girl, not acutely ill, complaining of pain in the abdomen. Menstrual history: Catamenia at thirteen and one-half years, always regular, five-weeks type, flow moderate in amount and lasting about five days. No dysmenorrhea. Last menstrual period was March 16, 1938.

\*Presented at a meeting of the New York Academy of Medicine, Section on Obstetrics and Gynecology, December 27, 1938.

## COMMENT

Probably it will be conceded that the complaint of this patient on her second admission, was due to the presence of a granulosa cell tumor. Recurrent, periodic, postmenopausal bleeding in a woman, aged 59 years, would, today, warrant an exploratory laparotomy. The finding of hypertrophic cystic endometrium would strengthen this conviction even without the evidence suggested by the enlarged uterus which had not been noted at the time of her first admission.

Granting this primary assumption, it would appear from the subsequent history of amenorrhea, two and one-half years in duration, that the small menopausal dose of radium effected a "cure" by causing regression of the tumor. That this effect was not complete, is obvious from the recurrence of symptoms and from the findings at operation. It would indeed be interesting to postulate what additional results would have been obtained had a much larger dose been employed, but further than this we cannot go.



Fig. 3.—The endometrium, showing cystic change.

The finding of an early adenocarcinoma in the endometrium proves to be an additional point of interest and introduces again the question of the carcinogenesis of estrin. We have observed this association in two additional cases of granulosa cell neoplasm, reported recently from this clinic. Finally, the good result obtained in this case emphasizes again the low grade of malignancy commonly demonstrated by granulosa cell tumors.

## SUMMARY

An additional case of granulosa cell tumor of the ovary is described. The postmenopausal bleeding produced by this tumor was arrested for a period of thirty-one months by the employment of 1,200 mg. hours of radium. The tumor again made itself manifest after this period and on removal, was found to be associated with an early adenocarcinoma of the endometrium. Recurrence of symptoms was not noted over a period of seven years of postoperative observation.

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*Microscopic.*—(1) Material from the larger cystic area of the left ovary shows various types of tissues, frequently in organoid arrangement, including cartilage, bone, skin and sebaceous glands, brain and ependymal structures, myxomatous and fibrous tissue and other glandular elements. (2) Tissue from the solid area of the

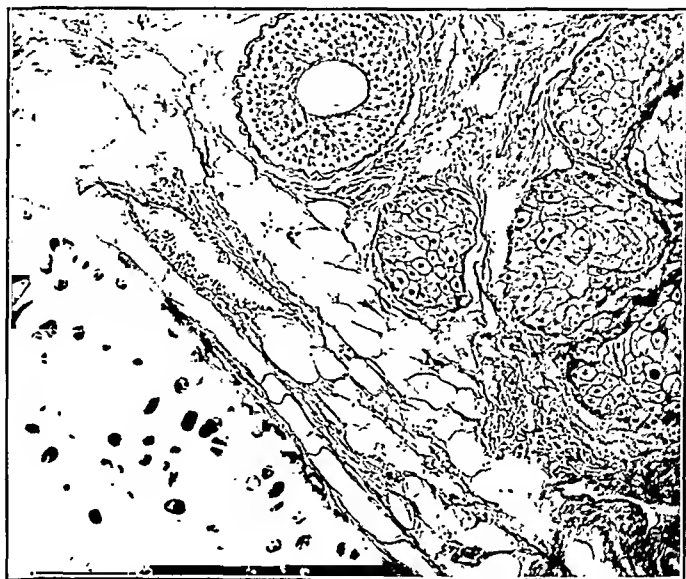


Fig. 1.—Photomicrograph of one area of the teratoblastoma exhibiting cartilage, sebaceous glands, hair follicles, fat and ependymal structures. Other areas showed various types of tissues arising from all three germ layers.



Fig. 2.—A typical section of the anaplastic papillary adenocarcinoma which occupied a large portion of the tumor.

left ovary shows a diffuse growth of anaplastic papillary adenocarcinoma with areas of cystic secretory activity and hemorrhage. (3) Material from the right ovary shows ectodermal elements of hair, skin, and sebaceous glands.

*Pathologic Diagnosis.*—Left ovary, teratoblastoma with papillary adenocarcinoma; right ovary, dermoid cystoma.

#### DISCUSSION

The teratoblastoma represented a malignant cystic lesion which, from the clinical course, appeared to have been larger at some previous time with spontaneous rup-

*Physical Examination.*—Palpation of the abdomen revealed a large asymmetrical tumor, extending from the symphysis to somewhat above the umbilicus. It was firm in consistency, irregular in contour and tender on palpation. The tumor was more prominent to the left, but extended for about two inches to the right of the midline. The entire abdominal wall was tense, but there was no rigidity present. Fluid wave was absent. Rectal examination revealed the lower pole of the tumor filling the entire left pelvis. To the right the cervix could be readily felt, and to the right of the cervix there was present a small mass, the exact size and consistency of which could not be definitely outlined.

*Laboratory Data.*—The urine was negative. Blood examination showed Hb. 80 per cent; red blood count, 4,200,000; white blood count 9,300, of which 74 per cent were polynuclear leucocytes, 20 per cent lymphocytes, and 3 per cent band forms. No other abnormalities were noted.

*Operation (I. S.).*—April 18, 1938: Bilateral salpingo-oophorectomy under general anesthesia. The abdomen was opened by paramedian incision. There was a small amount of free fluid in the peritoneal cavity. A large cyst presented, extending about half-way to the diaphragm and downward to the pelvis. The cyst was free of adhesions except for a firm band extending from its lower anterior wall to the bladder. This was transected. The tumor was freely movable and attached to the lateral wall of the uterus by a broad thick pedicle. The cyst was isolated by means of wet gauze pads. Owing to its size it was thought advisable to aspirate some of the fluid before removing it. A small trocar was inserted and only a small amount of bloody fluid was obtained, not sufficient in amount to warrant any further attempt. The abdominal incision was therefore enlarged, the cyst delivered, easily removed, and the pedicle stump covered by peritoneum.

The right ovary was palpated, found to be enlarged, freely movable and easily lifted out of the pelvis. It was about the size of an orange, firm in consistency with a fairly well-developed hematoma on its anterior surface. The entire mass was easily removed and the pedicle peritonized.

The uterus was small, freely movable, and appeared to be normal. Inspection and palpation of the entire pelvis showed nothing further of a pathologic nature. Since both tumors were well encapsulated, freely movable and had fairly large pedicles, it was felt that there was no reason for subjecting the patient to hysterectomy. The abdomen was therefore closed and the patient returned to bed in good condition. She made an uneventful recovery, and left the hospital on the twelfth day. She was subsequently referred for high voltage deep x-ray therapy.

*Pathologic Report.*—Gross description: Pathologic specimen (No. 13852) consisted of tubes and ovaries. The left tube measured 5 cm. in length and showed no gross pathology. Its ovary was enlarged and measured 17 by 15 by 6 cm. and was received partially opened. The surface was smooth and fibrous and exhibited congested veins with no evidence of previous perforation. There was a 4 cm. lobulated projection on the surface of the larger mass. On section of the whole ovary, it was seen to be a large, multilocular, cystic tumor which contained a heterogeneous mass of fluid, gelatinous material, yellowish, firm, opaque material, cartilage, bone and an encapsulated mass of reddish brown, friable tissue which occupied about one-third of its substance. The previously described projection on the surface, which seemed to be part of the outer shell, was a loculation which contained hair and sebaceous material, apparently the dermoid area associated with the larger teratomatous cyst. The inner surface of the larger cyst cavities presented several areas of focal sessile papillary proliferation. The third large loculation was filled with solid, friable, opaque and translucent material which was interspersed with numerous small cystic areas and hemorrhage.

The right tube measured about 4 cm. in length and showed no gross pathology. Its ovary measured 4 by 4 by 2 cm. and was received open. It had a multilocular cystic structure. Sebaceous material and hair arising from a nidus on the inner wall occupied the major cyst cavity. The remaining small portion of the ovary contained a hemorrhagic cyst and multiple small serous cysts.

remained at 2+. It was decided to induce labor by inserting a bougie. When this was attempted, it was found that the internal os could not be reached because of the markedly elongated cervix, so a small size No. 16 bougie was inserted through the cervix, with only moderate difficulty. The membranes did not rupture.

The bougie was left in place for twenty hours, and during this time the patient complained of severe pains but no uterine contractions could be felt. The abdomen was extremely tender and adequate palpation could not be done. It was decided to do a cesarean section because of severe pre-eclampsia and failure to establish labor by bougie insertion.

A midline incision was made and as the peritoneum was exposed, it was found to be very vascular and thickened. On opening into this, the fetal sac was entered directly and a viable 4 pound 9 ounce female child was extracted. The fetal sac was in the center of the abdominal cavity. The placenta was attached to omentum, ileum, ascending and transverse colon. There was no attachment whatsoever to the uterus or either of the Fallopian tubes. Because of the extensive attachments to the intestines it was decided to leave the placenta in situ. The uterus was the size of a three months' pregnancy. The fetal sac and peritoneum were fused, so they were closed together and without drainage.

The patient's postoperative course was uneventful; only on one occasion did the temperature reach 100.4° F. She was discharged on April 18, 1939, the eighteenth postoperative day, in good condition.

Nothing more was heard from this patient until May 12, 1939, when she returned stating that she had felt well after discharge for one week but gradually began to have loss of weight and appetite. On examination she was weak, pale, and the abdomen was greatly distended and was larger than a term pregnancy. In places this was dull to percussion and in other places tympanitic. Her temperature was 103° F. Blood count showed 60 per cent Hg; R.B.C., 3,000,000; W.B.C., 18,000; 88 per cent neutrophils. Impression was that there was a large accumulation of pus in the fetal sac.

She was given a 500 c.c. blood transfusion, and then the abdomen was incised in the midline and a large amount of pinkish, gray fluid drained (estimated 3000 c.c.). This was moderately foul in odor; there was also some gas escaped with it. Two large rubber drains were left in the abdominal wound. Bacteriologic studies of the fluid showed no growth on brain broth but *Staphylococcus aureus albus* after four days' growth on blood agar was found.

Following this operation the patient continued to run a temperature elevation and developed a phlebitis of her left leg. A semisolid mass could be palpated in the right upper and middle quadrant. This was considered to be at the site of the placenta and was thought to be another accumulation of pus. Consequently one week later an incision was made over the mass in the right upper quadrant. This was found to be the old placenta which was necrotic at the edges but intact and well encapsulated and was easily shelled out. The peritoneum was thickened and walled off from the peritoneal cavity. There was a direct communication with the lower abscess cavity, consequently the upper abdominal wound was closed and was allowed to drain through the lower incision.

The patient's course following this was uneventful. She was afebrile after the fourth day. She was discharged three weeks after the last operation. There was still a small draining sinus.

*Follow-up examination:* Aug. 10, 1939. Baby doing very well, weighed 13¼ pounds. Mother had no complaints; no abdominal pain or constipation. Left leg swelled when she was up for a long time.

*Physical examination:* Abdomen: No masses or tenderness; both incisions well healed. Pelvic: Outlet well supported. Vagina: Healthy mucosa, no discharge. Cervix: Slight central erosion; normal size. Uterus: Normal size, shape, position, and mobility. Adnexa: Normal. Left leg had slight pitting edema about the ankle.

ture or perforation and subsequent diminution in size. So far as could be determined at operation and from the pathologic study, there had been no peritoneal involvement by extension of the malignant process through the capsule or following rupture with dissemination of intracystic material. This fact, in addition to the time element, leads to the assumption that rupture probably occurred from the fluid part of the loculated cystic ovary. It also lends support to the belief that the solid carcinomatous portion of the tumor arose as an area of malignant metaplasia in a previously benign teratoma. Although this is an unusually rare occurrence, it is most probable in this instance because those teratoblastomas which are malignant from their inception usually exhibit early bilateral malignancy and rapid growth. The opposite ovary in this case showed only a benign dermoid cyst and no evidence of carcinomatous extension.

Although hysterectomy was not performed in this young woman, such complete operation with bilateral oophorectomy should be the usual policy in practice where ovarian cancer is found.

The patient has been subjected to high voltage deep roentgen therapy as a prophylactic measure against development of possible disseminated cancer cells. She is now free of clinical evidence of disease almost three years after onset of first symptoms and one year after operation. Her subsequent course is unpredictable, although at this time the outlook is favorable.

Grateful acknowledgment is made to Dr. Joseph Felsen, Director of Laboratories and Research, The Bronx Hospital, for his aid in the preparation of this paper and in the preparation of the photomicrographs with the technical aid of Mr. Thomas E. Ross, photographer to The Bronx Hospital Laboratories.

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## ABDOMINAL PREGNANCY REQUIRING SECONDARY REMOVAL OF THE PLACENTA

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THE following case history is reported because of its unusual sequela. The authors have not found an identical case reported in the English literature of the last ten years.

The patient was a 38-year-old, gravida iv, para iii, who was referred on March 28, 1939, for care and delivery because of toxemia of pregnancy. She stated that her last menstrual period was July 4, 1938, making her estimated date of confinement, April 11, 1939. For the last month she had had considerable swelling of her feet and ankles and for the past week had backache and some blurring of vision. Her blood pressure had been elevated for the last month. There had been severe abdominal tenderness and pain all during her pregnancy.

Her past medical history was irrelevant. She had had three normal pregnancies, the last one ten years ago.

Physical examination showed an extensive edema. Her face was puffy, hands were swollen, and there was 3+ ankle edema. The abdomen was of normal contour; not easily palpated because of edema of the abdominal wall. Fetal heart was heard in the left lower quadrant.

Vaginal examination revealed a normal-sized pelvis, cervix large, and very edematous. External os could be seen at the introitus and was two fingers dilated. Blood pressure was 175/90. Patient was admitted for treatment of pre-eclampsia.

Urine showed 2+ albumin, blood count, 91 per cent Hg; R.B.C., 4,800,000; W.B.C., 8,600; nonprotein nitrogen, 33; uric acid, 6 mg. per cent.

This patient was given intensive treatment for four days for pre-eclampsia, but did not respond. Blood pressure remained around 175 to 180 systolic, and albumin

wound was closed with two layers of continuous chromic 2 catgut through the muscle and one continuous chromic 2 suture approximating the serosa and adherent parietal peritoneum. Abdominal wall was closed with interrupted silk worm gut in skin. The patient and baby made an uneventful recovery and were discharged well on the sixteenth postoperative day.

This patient, evidently not safed with eleven laparotomies, will enter the hospital in the near future for a bilateral inguinal herniorrhaphy.

I wish to acknowledge the valuable assistance of Miss Helen J. Crowley, of the Social Service Department of the Boston City Hospital, in tracing this patient and compiling the records.

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47 BAY STATE ROAD

## IMPROVED INSTRUMENT FOR TUBAL INSUFFLATION, SALPINGOGRAPHY, AND AEROUTEROGRAPHY\*

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THE instrument consists of a straight cannula about 10 inches in length and  $\frac{1}{8}$  inch in diameter. A solid conical metal obturator surrounds the shaft, and is permanently attached about  $\frac{1}{4}$  inch from the distal end. The width of the base of this obturator is  $\frac{1}{2}$  inch, its height about  $\frac{5}{8}$  inch. At the other end of the cannula there is a regular Luer hub. A one-way stopcock is fastened to a hole drilled on one side of this hub. The stopcock has a projection which permits the attachment of rubber tubing. A metal ring on the hub serves as a convenient finger grip (Fig. 1).

#### TECHNIQUE

1. *Tubal Insufflation*.—The cervix is exposed and cleansed by wiping with cotton pledgets. The canal, portio, and vaginal mucosa are painted with tincture of iodine. The distal end of the sterilized cannula is introduced directly into the cervical canal. At the proximal end, a 30 c.c. syringe with the piston fully withdrawn is attached to the Luer hub and tightened with a quarter turn of the syringe barrel. The stopcock is opened and a manometer attached to the projection of the stopcock by a short piece of rubber tubing. Inward pressure is exerted on the cannula against the external os to effect firm occlusion of the external os by the obturator. Maintaining the inward pressure, air is slowly injected by pressure on the plunger of the syringe. The interpretation of the test has been outlined in a previous article.<sup>1</sup>

2. *Salpingography*.—The technique is the same as for tubal insufflation except that no manometer is necessary. The stopcock is closed, and 10 c.c. of iodized oil or skiodan acacia mixture are injected. The solution is injected fractionally or completely, and followed by x-ray pictures.

A twenty-four-hour check-up plate is taken afterward.

3. *Aerouterography*.—The preparation is the same as for tubal insufflation, except that a tenaculum is placed on the cervix to hold the cervix and uterus in proper position. Without the traction on the tenaculum, the subsequent x-ray pictures show distortion of the uterine position.

I personally prefer a 100 per cent skiodan solution for this purpose.

The syringe containing 10 c.c. of the solution is attached to the Luer hub and the stopcock closed. Four cubic centimeters of the solution are injected and an x-ray exposure made. The stopcock is then opened allowing the solution to drain

\*Instrument supplied by Research Department, Becton, Dickinson & Co.

## CESAREAN SECTION FOR THE NINTH TIME

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IN 1933 when I performed the ninth cesarean section on this patient, who was then 38 years old, she was still desirous of further propagation and apparently well able physically to withstand more pregnancies. Therefore, I have postponed reporting this case until I was reasonably certain she was beyond the age wherein she might surpass her unusual record of multiple cesarean sections.

A careful search through the literature disclosed seven as the highest incidence of cesarean section on one patient as yet reported.<sup>1</sup>

D. C., a white para ix (Hospital Record No. 724592), aged 38 years, entered the Boston City Hospital on Oct. 5, 1933, in mild labor. Her medical history was uneventful. Past surgical history: Cholecystectomy, 1919, appendectomy, 1929. Past obstetric history: (1) Sept. 23, 1912, at New England Sanatorium, Melrose, Massachusetts. Classical cesarean section because of bony dystocia after several hours' test of labor. Normal convalescence. (2) Oct. 27, 1914, at Tewksbury State Hospital, Massachusetts. Classical cesarean section at term. Normal convalescence. (3) April 3, 1916, at Tewksbury State Hospital. Classical cesarean section at term. Normal convalescence. (4) Nov. 9, 1917, at Tewksbury State Hospital. Classical cesarean section at term. Normal convalescence. (5) Oct. 7, 1919, at Tewksbury State Hospital. Classical cesarean section at term. Normal convalescence. (6) Jan. 10, 1922, at Boston City Hospital. Classical cesarean section at term. Normal convalescence. (7) July 21, 1924, at Boston City Hospital. Classical cesarean section at term. Slight wound sepsis. Otherwise normal convalescence. (8) April 17, 1932, at Boston City Hospital. Low cervical cesarean section at eight months because of premature partial separation of the placenta, with death of the fetus. Normal convalescence.

*Present Pregnancy.*—Last menses began Jan. 5, 1933. Due Oct. 12, 1933. Patient had received no prenatal care (as was her custom). No toxic symptoms. No flow. Baby active. Irregular mild labor pains started about two hours before admission.

*Examination.*—Patient in mild first stage labor with pains every six to eight minutes lasting twenty-five seconds. Blood pressure 112/68. Urine negative. Uterus at term, vertex floating, left position. Fetal heart in left lower quadrant, rate 138, of good quality. Her pelvis was of the justo minor, generally contracted type with an intercrystal diameter of 25 cm., an interspinous of 20 cm., and external conjugate of 17 cm. The symphysis was narrow and the subpubic arch angulated, suggesting a male type of forepelvis. The intertuberosus diameter of the outlet was 8 cm. and the posterior sagittal 9 cm. There were four well-healed lower abdominal median and paramedian scars, a firm low right rectus as well as a high right rectus scar. Rectal examination found the cervix partly taken up, one finger dilated, membranes intact, vertex floating.

*Operation.*—Under gas-oxygen-ether anesthesia a left paramedian scar was resected, exposing a thick mass of dense fibrous scar tissue extending from the subcutaneous plane to the peritoneum. The lower two-thirds of the anterior wall of the uterus were so firmly adherent to the parietal peritoneum that separation was not only impossible but unwise since the uterus could be readily opened with the surrounding peritoneal cavity well walled-off by dense adhesions. A classical type of cesarean section was done and a 7 pound 4 ounce baby extracted without difficulty. Palpation of the uterine wall with the hand in utero after the placenta was extracted disclosed no evidence of any thinning from previous scars. The uterine muscle acted well after intravenous pituitrin and intramuscular ergot. The uterine

## AN UMBILICAL CORD SHIELD

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A SUITABLE dressing for the umbilical cord has long been a troublesome nursery problem. The usual practice is to use a small pad of gauze held in place by a roller bandage around the abdomen. The objection to this method in ordinary use is that as often as the baby's diaper is wet the dressing on the cord is wet and, inasmuch as we are particularly interested in promoting the drying of the cord, this constitutes a definite disadvantage that necessitates either frequent changes in the dressing or putting up with a moist cord stump. The method described here has been found to obviate these disadvantages.

A cord protector was devised from a transparent plastic material known as "lucite." This protector consists of a plate of lucite  $3\frac{1}{4}$  inches square. This plate is molded so that it represents a section of the circumference of a cylinder 8 inches in diameter. The center of the plate is then molded so as to create a bulge  $1\frac{3}{8}$  inches deep. The base of this bulge is of such a diameter as to leave a margin of  $\frac{1}{2}$

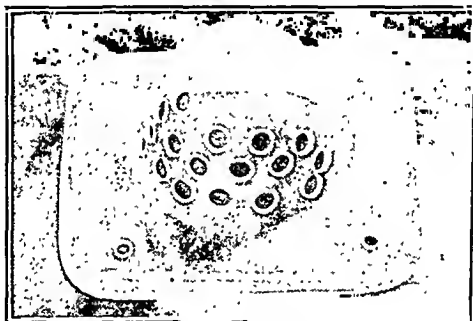


Fig. 1.

inch all around. Numerous perforations,  $\frac{3}{16}$  inch in diameter, are then put on the upper and lateral aspects of the shield. The part that lies ventral and inferior, that is to say, in the direction of moisture and contamination, remains without perforation.

In using this shield the cord is first tied or clamped, and the shield is then placed over the stump with its curvature conforming to the curvature of the baby's abdomen. It is then fastened in place with adhesive or cellulose tape.

The material from which the shield is constructed softens at  $235^{\circ}$  F. It is not appreciably affected by acid or alkalies, is practically noninflammable and nonbreakable and, at the same time, is as transparent as glass. It is soluble in acetone.

The advantages of this method are (1) that it provides free ventilation for the cord, thus hastening the drying process, (2) the cord is visible at all times so that its condition can be determined at all times without necessitating the removal of the dressing, and (3) it is protected from the moisture of the diaper.

This device is made by the Ford Ceramic Arts, Columbus, Ohio.

out of the cannula and the uterine cavity. The cannula may even be withdrawn to allow more complete evacuation of the solution from the uterine cavity. After emptying, another x-ray picture is taken. Another syringe containing air is then attached to the hub of the cannula. Air is injected until a sensation of tension is transmitted through the plunger of the syringe. Maintaining the same pressure, another x-ray picture is taken. This picture shows a contrast delineation of the interior of the uterus.

If desired, the syringe containing the skiodan solution may now be reattached to the cannula and the balance of the solution injected. This is also followed by an x-ray picture. The cannula is then withdrawn. Fifteen minutes later a follow-up x-ray is taken.

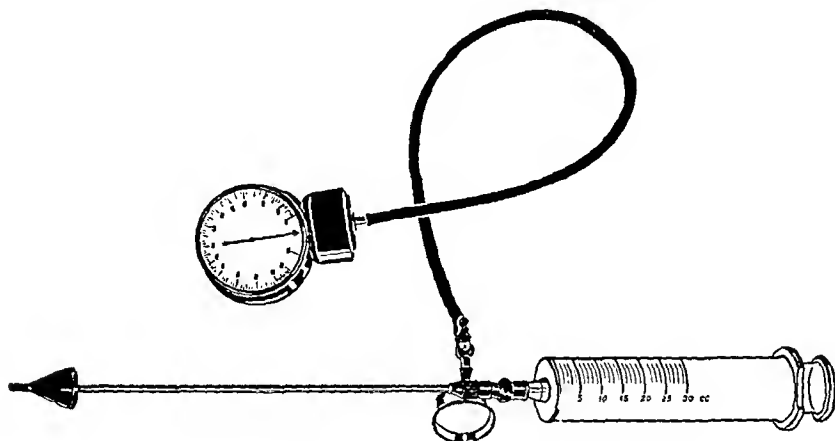


Fig. 1.—Instrument assembled for tubal insufflation.

The addition of the latter part of the procedure, that is, from the injection of the balance of the skiodan onward, permits of a combination of aerouterography and salpingography at the same time.

The findings in patients in whom this technique has been used will be reported in a subsequent communication.

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151 WEST 77TH STREET

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The author gives the following suggestions for proper collection of seminal discharge: Condoms used for collection of seminal specimens should be free from spermicidal power as far as possible. The sheet should be free of starch grains, but may be dusted with French chalk or lycopodium. Within at least five minutes after ejaculation the semen should be transferred to a clean glass specimen tube provided with a cork previously soaked in melted paraffin. The tube then is kept at room temperature; body temperature is most undesirable, because spermatozoa use up their store of energy by activity before examination and bacteria multiply. The tube should not be kept in a refrigerator before examination.

HUGO EHRENFEST.



been made possible by the scientific developments in pediatrics, as well as by the untiring efforts of a well-trained nursing personnel, in making these discoveries operative.

On May 14, 1914, in Italy, 5 infants, all alive and viable, were born to Rosa Salemi, 40 years old. The first and second lived four days; the third, five days; the fourth, seven days, and the fifth, eight days. It is the opinion of the attending physician that if there had been greater care and assistance on the part of the attendants to whom the children were entrusted, they might have lived as did the Dionne quintuplets.

In the progress of pediatrics, a simple formula for the care of premature infants has been developed, which was followed to the letter from the very beginning in the care of the Dionne quintuplets. This formula, when applied to the care of premature infants in general, and a large percentage of multiple births is in the premature class, may do much to reduce the mortality among these tiny, frail babies. The formula was the one adopted in the care of the Dionne quintuplets including the following:

Premature babies must be kept warm from the moment of birth. They should be kept in surroundings in which the temperature is at least 80° F. They should not be exposed to a temperature lower than this for even an instant. Once a premature baby loses body heat, the strength may be so decreased that the chances of survival may be quickly and completely lost.

The premature infant must be properly fed, and the best food, by all means, is breast milk, if it can possibly be obtained. Of course, vitamins in the form of orange juice and of cod-liver oil, or some similar substance, must be started at the proper time. Every effort must be made to overcome anemia, which is a definite hazard to the premature infant. This can be done by giving egg yolk or some iron preparation.

Premature babies must be protected from infection and therefore must be kept away from any one who is sick. No one should be permitted to handle a premature baby, or even to enter the baby's room without first putting on a clean gown and washing the hands with soap and warm water. Many advocate also the wearing of a face mask by all the attendants.

Oxygen is almost an essential in the care of most premature infants and the method of use will depend on the degree of prematurity and the infant's condition. There can be no doubt that many infants have been saved by the continuous supplying of oxygen. Premature babies develop cyanosis, because very often the lungs are inadequately developed. By supplying oxygen through a face mask, or preferably through a small nasal catheter, or in an oxygen bed if it is available, premature infants have been tided over these cyanotic attacks. In the case of the Dionne quintuplets we used cylinders containing 95 per cent oxygen and 5 per cent carbon dioxide.

Before we obtained oxygen, we had been giving the babies a drop or two of rum when they required stimulation. However, when the oxygen came, we practically stopped giving the rum. Some doctors at that time wrote me to suggest that I should have used brandy, not rum. Well, the fact is that I did not have any brandy. So I had to use what was available.

The eternal vigilance of well-trained nurses overshadows almost every other essential in the care of the premature infant. Premature babies should be under the care of such nurses throughout every minute of the twenty-four hours. During the few minutes when the nurse may be absent from the baby's bedside, an attack of cyanosis, or some other disturbance, may develop, that can prove so damaging that survival is endangered.

The things which are not done for these babies are almost as important as the things which are done. The premature infant is frail, does not stand handling, and must be left undisturbed most of the time. Unnecessary manipulation and over-treatment may be as damaging as neglect.

The Dionne quintuplets are well into their sixth year of life. However, their care after the first year has been no different from that ordinarily supplied

# Department of Maternal Welfare

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CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

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## THE SURVIVAL OF THE DIONNE QUINTUPLETS\*

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THE Dionne quintuplets are unique because they are the only entire group of quintuplets that have survived for any great period of time. Prior to this event, the longest period of time over which any single quintuplet had survived was fifty days. This record was established by one of a group of quintuplets in 1866, in Lisbon, Portugal. The Lyon quintuplets also survived for a short time. They were born in Kentucky in 1896. The first infant died after four days and by the fourteenth day all had died. It is estimated that quintuplets occur once in every 57 million births.

In the last several centuries, about 60 cases of quintuple births have been reported, all of which are at least fairly well authenticated. However, complete data are lacking. It is known, however, that survival for a few days, hours, or even for a few minutes only, did not occur in any others than those just mentioned.

There are a number of interesting facts which have been garnered about these 60 quintuple births. In 28 of these 60 cases, the age of the mother is known. Quintuplets who do not look alike and are of different sex, are called fraternal. These infants develop from several different eggs. Quintuplets who do look alike and are all of the same sex are called monozygotic. They all come from one egg. The Dionne quintuplets are of this type. Of the 28 mothers of quintuplets whose age is known, the older mothers gave birth to the fraternal sets, and the younger ones to the single-cell type. Only 2 of the 60 births of quintuplets were in mothers having their first baby. The greatest number of quintuplets were born as of the third, fourth, or later pregnancies. From a study of these quintuplets it seems that when the infants were unlike each other, that is, fraternal sets, there was an hereditary tendency in the family for having multiple births, such as twins and triplets. On the other hand, when the sets of quintuplets were like each other, there was no hereditary tendency to multiple births.

In the case of the Dionne quintuplets, there is no history of multiple births, except in distant relatives. From this fact it appears that there is less than the usual chance that there will be twins or other multiple births if there are offspring from the quintuplets.

Besides being of the same sex, the Dionne quintuplets are of the same blood group; are nearly indistinguishable in eye color and pattern, in hair color, and in the amount of skin coloring. The children also share certain rare features, such as syndactylia or webbing of the second and third toes. Throughout the set, the two hands of any one of the children are less like each other than is one of her hands like the corresponding hand of her sister. For example, Marie's right hand and Yvonne's right hand are more alike than are Marie's own right and left hands. This close resemblance which the quintuplets show would not be expected unless all five came from the same egg. Three other of the sets of quintuplets reported appear to have been similarly identical. Thus, the Dionne quintuplets are not unique in this respect; only their survival remains unique in the annals of medicine. This survival, in large measure, has

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\*Presented at a public meeting of the First American Congress on Obstetrics and Gynecology, September 13, 1939, at Cleveland, Ohio.

The slightest change in temperature caused alarming reactions in the babies. A temperature of about 92° F. made their faces flush, and made the infants pant. A temperature of only several degrees below ninety immediately brought on a bluish tinge around the nostrils and caused a rapid increase in breathing.

The babies developed frequent sinking spells. It was necessary for the nurses every minute of the day and night to be constantly on the alert for the development of these spells and to give oxygen at once. This is what I mean by constant watching on the part of the nurses. They did not remove their eyes from these babies for even an instant during the early, critical days.



Fig. 2.—The quintuplets at two months. Left to right: Marie, Emelie, Cecile, Annette and Yvonne.



Fig. 3.—Under the sun lamp at 6 months. Left to right: Emelie, Cecile, Marie, Annette, Yvonne.

The babies were kept in the incubators until they reached the weight of six pounds. When they were five pounds in weight the incubators were used as cots, and the extra heating was stopped.

For the first twenty-four hours nothing was given to the babies by mouth but warm water every two hours. After this twenty-four-hour period, feedings were started. The milk was given to them from a medicine dropper. By the fourth day the infants were receiving breast milk boiled, full strength, and from that time on until the fifth month, the only milk the babies received was breast milk.

to any well-cared-for infant. It is during the first year and, particularly, the first few weeks that special care is so necessary for premature and tiny infants. Once they have passed through the first year, their development, both physical and mental, goes on in the usual way.

The Dionne quintuplets, 5 tiny girls, were all thrust into the world within a period of an hour. Who was born first and who last is of no significance, except perhaps as a matter of sentimental curiosity. There was too much confusion, too much excitement at the sudden birth of these five babies, in a dark room, only dimly lighted by an oil lamp, to give time for identification or much investigation. Then, too, the mother, whose condition was dangerous and whose very life was at stake, remained the first consideration. As a matter of fact, at first the babies were designated only by letters, A, B, C, D, and E, until names were decided on.



Fig. 1.—Bath time for Marie, aged 2 days.

Of the quintuplets, Marie was the smallest and weakest and Emilie the next smallest. The babies, soon after birth, looked like plucked, wrinkled chickens. Their tiny hands moved in jerky, pathetic movements. As soon as possible after the birth of these babies, some one was sent over to a neighbor's for a basket and returned with an ordinary butcher's meat basket. Heated blankets were placed in the bottom of the basket, and the babies, who right after birth were wrapped in warm coverings made from any old pieces of cloth available, were placed in the basket. Top blankets, which were first warmed, were put over them. These top blankets were changed frequently. In this way, heat was supplied to the infants constantly. Three hours later the babies were taken out of the basket singly, placed on a warm blanket, gently rubbed with warm olive oil, and immediately returned to the basket. All of the early care was given on the nurse's lap. She sat directly before an open oven, which obviated any chance of the infants being chilled. A larger basket was obtained on the second day and hot-water bottles were located and put into the basket. This made it easier to keep the temperature at the proper level. On the third day an incubator arrived from Chicago. This was used to house the three weakest of the infants. There was no room for the others.

After a week, a second incubator arrived, and, finally, there was one for each baby. The temperature in the incubator was kept between 87° and 90° F. at first. As time went on, the temperature was gradually lowered and maintained at 84° F.

As many believe that extra moisture is helpful for premature infants, this was supplied by soaking sponges in hot water. The amount of moisture in the air was kept as closely as possible between 50 and 55 per cent of saturation; that is, 55 per cent of the amount of water that the air would hold.

was necessary. Second, there was a steadfast refusal to indulge in experiments of any kind in their care, although temptations to do so were great. Third, no unnecessary handling was permitted at any time. Fourth, continued vigilance, day and night, every minute, on the part of the nurses, assured that every emergency would be met properly and that the babies would be given at the right moment those things which they needed to tide them over a critical period.

Application of a similar simple formula in the care of any premature baby should give the baby the maximum chance of living, and should lead to a reduction in the infant death rates.

The Quintuplet Guardianship Act passed by the Ontario Government, placed the Dionne quintuplets under control of the Crown and appointed a Guardianship for them until they reach the age of eighteen. The guardians are, first, the father, then Judge Valin, a retired jurist of North Bay, the Official Guardian of Ontario, and myself. The guardians meet once a month. They have full control of all business affairs and other matters pertaining to the children's estate. They make contracts, pay expenses, and in general, carry on the duties associated with the children's care and welfare. That this plan is successful is attested to by the health and happiness of the children. All matters concerning the health and well-being of the children are left to me.

Modern pediatrics teaches us that if the premature baby is to have his chance for life, these are the things he needs:

1. Constant maintenance of body heat.
2. Provision of breast milk without meddlesome experimentation with other foods.
3. Giving of oxygen at every critical moment during the twenty-four hours.
4. Avoidance of infection.
5. Vigilant nursing by well-trained nurses, who do not relax in their care for even a moment, working under the constant direction of the doctor.
6. Knowing what not to do, which is at least as important as knowing what to do.

These are the things which undoubtedly made it possible for the Dionne quintuplets to be the first quintuplets to survive, and this without costly or complicated equipment. But it did require eternal vigilance without a moment's cessation, by well-trained personnel.

Past failures with quintuplets, in my opinion, may be charged to the momentary cessation of vigilance in any one of these essentials. With the valuable advice of so many fine experts at my disposal, the task of caring for the five girls has been made easier.

I would like to mention the numerous men of both Canada and the United States, who have helped me with their advice and their services from time to time. However, the list would be too long to include here. But, I cannot let this opportunity pass without telling you about the part played by Dr. Herman N. Bundesen, President of the Board of Health of the City of Chicago. As soon as he heard the news of the quintuplets' birth, he called me on the long-distance telephone and gave me valuable advice. He also dispatched to us by aeroplane our first supply of mother's milk. I also want to mention Dr. Alan Brown, one of Canada's outstanding pediatricians. He arranged for a continuous supply of mother's milk for us from Toronto, and he has come to our assistance many times when we have needed him.

I have also had the services of my brother, Dr. William Dafoe, at my disposal; I have used them many times.

It is my hope that our experience with the Dionne quintuplets will be of some service in guiding others who are confronted with similar problems in the care of premature babies.

Our experiences with the quintuplets lead us to believe that, when such procedures as we adopted are followed, there may be a material reduction in deaths, especially of premature babies, whose death rate is one of the major problems confronting us in reducing infant mortality.

On the fourth day the babies were able to take their nourishment from a Breck feeder, which method was continued until the babies grew strong enough to take their feedings from a bottle, at six weeks of age. The two-hour feeding interval was gradually increased to two and a half and then to three hours, until at ten months of age, the babies were fed four times a day.

For the first three and a half months the nursery for the quintuplets was included in the limited space provided by a house of three rooms and a summer kitchen on the ground floor, and three bedrooms upstairs. In these rooms dwelt the family, consisting of the father, the mother, five children, two maids, one janitor, two nurses, and five premature babies. The equipment available for caring for the quintuplets was limited. Yet, the constant vigilance of the nurses and the application of simple rules, together with the inherited vitality, permitted these babies to live.

The Dionne quintuplets, it is estimated, were born at about the seventh month of pregnancy. The combined weight at the time of birth as shown by weighing the infants on an ordinary household scale, was about 13 pounds, 6 ounces. After about a week, when weighed on an accurate scale, the combined weight of the five babies was less than ten pounds. The two heaviest weighed a little over two pounds each. Cecile, Emilie, and Marie weighed less than two pounds. Marie, the smallest, weighed only one pound, eight and one-half ounces.

After the confusion of the first week passed, the organized plan for the care of the quintuplets began to function more smoothly, and the opportunity presented itself to do other less necessary but still important things. The doors and windows were screened to shut out flies and mosquitoes. The babies' room was carefully gone over and every possible measure of aseptic technique, such as hand washing, proper waste disposal, and suitable ventilation, was provided. The rest of the children of the family were removed to other quarters, as several of them had developed bronchitis, which it was thought would be dangerous to the babies. No one entered the small nursery but the nurses, the doctor, and occasionally, the parents. Every one without exception, who crossed the threshold, wore a mask over the face, because we wished to do everything possible to help protect the quintuplets. They were kept away from as many sources of infection as was humanly possible. All hands touching them at any time were well washed with soap and warm water. Every care was taken to prevent exposure of these babies to infection, and the results seem to have justified the means.

The quintuplets were given the only natural, correct diet on which they could have a chance of surviving, breast milk. If mother's milk had not been secured in sufficient quantities at the right time, I feel certain the quintuplets would not have lived.

In spite of their prematurity, these five girls have progressed rapidly in physical development, so that now they have reached or exceeded normal levels for height and weight. Their general health and development have been normal, and there is no evidence of any physical or mental abnormality or subnormality as a result of their premature birth.

They have had setbacks, it is true. In the early fall of 1934, every baby in turn suffered from a severe type of intestinal infection, which developed suddenly. Improper sterilization of the diapers was considered a possible source for spreading the infection, but where the infection came from originally has not been determined. In recent years outbreaks of this sort in newborn nurseries all over the United States and Canada have not been unusual, nor has their true cause been determined as yet.

Anemia, which was present in the babies before this infection, became more marked after it. Therefore, small doses of ferrous chloride were given to the babies three times a day, in their feedings, and these were kept up until the infants were over one year old. Orange juice, cod-liver oil, cereals, vegetables, and other necessary foods were added to the diet of the infants as their development warranted.

Carefully observed regularity has been the essential principle in the later general care of these children. If there are any items in the care of these babies which deserve stressing, they are these: First, no fancy or unusual equipment

# Department of Reviews and Abstracts

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CONDUCTED BY HUGO EHRENFEST, M.D.

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## Selected Abstracts

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### Carcinoma

Imamura, S.: Heredity in Patients With Carcinoma of the Uterus, *Jap. J. Obst. & Gynec.* 21: 127, 1938.

Imamura investigated the heredity of all the patients who entered the Kyoto Imperial University Hospital during the years 1923 to 1934 with carcinoma of the uterus. He found a family history of cancer in 9.4 per cent of all the patients who had tumors of the uterus. Of the ancestors who had carcinoma, it was the mother in 33.7 per cent and the father in 24.3 per cent. Next in order were aunts, sisters, brothers, grandfathers, grandmothers, and uncles. The final analysis proved that the maternal relatives supplied 58.5 per cent of the familial cases of carcinoma, whereas the paternal relatives furnished only 41.5 per cent. The organ most involved in the relatives are in the order of frequency: the stomach (47.4 per cent), uterus (33.7 per cent), esophagus, liver, and intestines.

The author's incidence of family carcinoma approximates the figures reported by Schroeder (8.2 per cent), Gusserow (10 per cent), and others. The author found that a woman with carcinoma of the uterus transmits the tendency to cancer to her descendants, and the latter if females tended to have cancer in the uterus more often than in other organs.

J. P. GREENHILL.

Béclère, C.: The Frequency of Cancer of the Body of the Uterus After the Menopause, *Compt. rend. Soc. Franc. de Gynec.* 8: 99, 1938.

There exist two opinions concerning the frequency of carcinoma of the uterine body after the menopause. One is that when a woman begins to bleed after the change of life the chances are nine out of ten that she has a cancer of the body of the uterus. It is therefore useless to attempt to make a more exact diagnosis. The uterus should be removed. The second opinion is that only about 50 per cent of women who bleed after the menopause have cancer. To this opinion the author subscribes and he has collected from the literature reports of 1,203 cases of bleeding after the menopause. Cancer was present in only 40 per cent of these collected cases. The incidence of cancer in the individual series varied from 33 to 67 per cent. These statistics provide a good reason for not performing a hysterectomy routinely when women bleed after the menopause. In all cases a biopsy should first be performed and if cancer is found then and then only should the uterus be removed.

J. P. GREENHILL.

Oleh, Isaac Y.: Menopausal Age in Women With Cancer of the Breast, *Am. J. Cancer* 30: 563, 1937.

Combination of available statistics seems to show that about 71.7 per cent of women pass through the menopause between the ages of 40 and 50. If one notes the menopausal age of older women with mammary cancer, one is immediately struck with the greatly increased percentage who have delayed menopause.

Investigating the age of menopause in 342 women over fifty when first seen for a breast cancer, Oleh found that among them were 54.7 per cent who either were still menstruating or had passed through the menopause after the age

# Society Transactions

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## OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF MAY 4, 1939

Report of a Case of Calcareous Degeneration in Uterine Fibromyoma. Dr. H. J. Sangmeister.

Acute Inversion of the Puerperal Uterus. Drs. W. B. Harer and J. A. Sharkey. (J. A. M. A. In press.)

Analysis of 1,000 Consecutive Stillbirths in the Philadelphia Area. Drs. Arthur First, John Sharkey and Thaddeus L. Montgomery. (Report of a special committee.) (For original article see "The Child," published by the Federal Children's Bureau, September, 1939.)

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Hildebrandt: Significance of Achylic Chloranemia (Essential Hypochromic Anemia) in Gynecology, Arch. f. Gynäk. 165: 164, 1937.

Knowledge about achylic chloranemia is not sufficiently disseminated and the disorder does not receive the attention it deserves. The varying interpretation of the leading symptoms is the reason why so many different terms have been applied to the disorder which is much more frequent in women than in men. The patients frequently complain of fatigue, lack of energy, palpitation, tinnitus aurium, attacks of fainting, painfulness of the bones, loss of weight and gastrointestinal disturbances, such as lack of appetite, flatulence, constipation or, more frequently, diarrhea.

The objective symptoms are similar to those of pernicious anemia: there are changes in the lingual mucosa, trophic disturbances in the appendages of the skin, particularly of the nails, and rhagades. The skin is often pale white. The chief symptom of achylic chloranemia is a disturbance in the secretion of the gastric juice. Examination of the blood is of great importance for the diagnosis of the disease.

The author emphasizes that menstrual anomalies and genital hemorrhages are likely to appear during this type of anemia. Schulten, on the basis of 50 cases, estimated the incidence of severe menstrual hemorrhages in achylic chloranemia at approximately 75 per cent. Iron therapy is the method of choice, reduced iron, 1 gm. three times daily, and to intensify the action of the iron, hydrochloric acid is added. This therapy must be continued until a considerable improvement is noticeable in the blood status. The menstrual disturbances or genital hemorrhages that may exist improve simultaneously with the blood status.

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was present in between 14 and 15 per cent. The frequency of syphilis in the other patients in his clinic was only 1.6 per cent. The author believes that syphilis plays a rôle in the etiology of carcinoma of the cervix. However, syphilis only gives the impetus for the development of cancer. The prophylaxis and treatment of syphilis in women will reduce the number of cases of cancer of the cervix.

J. P. GREENHILL.

**Belonoschkin, B.: The Rare Occurrence of Adenocarcinoma of the Cervix During Thyrotoxicosis, Klin. Wehnschr. 27: 1117, 1938.**

The author describes the occurrence of an adenocarcinoma of the cervix in a patient suffering from an acute thyrotoxicosis and comments on the rarity of the combination of these two conditions. The thyrotoxicosis contraindicated surgical intervention, and the patient was given combined radium and roentgen irradiation. A fatal outcome resulted from the pyometra and pyosalpinx which followed. The endometrium which had been recently subjected to this irradiation showed marked inflammatory reaction to the irradiation plus many areas of local necrosis. Some areas showed a complete disappearance of the endometrium. Irradiation thus produced complete endometrial atrophy in a comparatively short space of time. The author cites two additional cases that bear out this observation. The author then attempts to show that thyrotoxicosis prevents follicle hormone formation. Since it is this latter which stimulates malignancy by virtue of its carcinogenic properties, its inhibition by hyperthyroidism results in the rare occurrence of simultaneous thyrotoxicosis and genital malignancy.

RALPH A. REIS.

**Schiller, Walter: Early Diagnosis of Cancer of the Cervix Uteri, New England J. Med. 218: 878, 1938.**

The human cervix uteri consists of two entities, the external os and the internal os. By naked-eye inspection the external os is defined as that part between the narrow cervical canal and the surface of the vaginal portion. This is called the anatomic external os. By microscopic examination, the external os is defined as that point where the nonhornified stratified squamous epithelium of the portio meets the high columnar mucinous epithelium, containing many glands, which lines the cervical canal. This the author calls the histologic external os.

When the cervical mucous membrane is not limited to the cervical canal but extends out to cover, in varying degrees, the area about the external os, there is an abnormality which occurs in a certain disturbance of fetal development. Only a small percentage of all women retain this congenital eversion throughout life.

On the other hand, in hypoplastic individuals with genital infantilism, it is found that the squamous epithelium of the external os ascends into the lower part of the cervical canal, occasionally up to half or even three-fourths of its length. This variation is of great practical importance in certain cases of carcinoma. Since carcinoma of the squamous epithelium generally begins next to the high columnar epithelium, the greater part of the initial carcinoma in such cases may develop by carcinomatous transformation of the squamous epithelium which lines the cervical canal.

The most frequent lesion of the cervix is erosion. By this term is meant a defect only in the epithelium as compared with an ulcer, in which the underlying connective tissue is also defective.

The precipitating cause of most of the erosions is the macerating influence of a discharge. This accounts for the fact that in nearly all cases of erosion a final and permanent healing can only be achieved when the causal cervicitis has been cured. In the healing of an erosion at the histologic os, an activity of both types of epithelium is observed: the columnar from the cervical canal and the squamous from the periphery are trying to establish themselves on the free and naked surface of the erosion. The columnar epithelium, which consists of one row

of fifty. That is, as compared with normal women in this group almost five times as many had a delayed menopause. He refers to recent reports of delayed menopause in cases of adenocarcinoma of the uterus, suggesting the advisability of artificial x-ray termination of unduly prolonged ovarian activity. Thus Olch arrives at the conclusion that an artificial menopause at some arbitrary age between 48 or 50 might possibly be of prophylactic value against the formation of a mammary cancer.

HUGO EHRENFEST.

Stevenson, Charles Summers and Scipiades, Elemer, Jr.: *Non-Invasive Potential "Carcinoma" of the Cervix*, Surg. Gynec. Obst. 66: 822, 1938.

Cancer is the second most frequent cause of death in the western world; cancer of the uterus is responsible for one-third of the cancer deaths in women; 90 per cent of uterine cancer arises in the portio of the cervix and is thus easily accessible for examination and study. The most favorable statistics from the treatment of cancer when it is limited to the portio of the cervix show a 52 per cent cure, while not more than 20 per cent of all cervical cancers have a five-year cure. Schottlaender and Kermauner (1912) and Schiller (1927) have described and called attention to a form of superficial non-invasive cervical "carcinoma." Schiller considers and treats it as definite carcinoma. The authors present 18 cases for which one of them (C. S. S.) has proposed the name "non-invasive potential 'carcinoma' of the cervix." In 1 patient (Case 2) the "carcinoma" remained non-invasive for eight years and one month, following which it developed into a clinical carcinoma and finally caused the death of the patient. A second patient (Case 13) died of pernicious anemia three years after the first biopsy examination revealed a non-invasive potential "carcinoma." Serial sections of this cervix revealed that invasion had taken place shortly before death.

WM. C. HENSKE.

Emge, Ludwig A.: *The Significance of Estrogenic Hormones in Carcinogenesis*, West. J. Surg. 47: 107, 1939.

Certain recent studies of mammary cancer in mice suggest that estrogenic hormones may have a more important part in the mechanism of carcinogenesis than heretofore shown for other hormones. In the light of modern research, it is no longer tenable to speak of cancer as a single disease, or as having a single cause. The causes vary with the types of cancer, the organs, and the species.

Experiments made by Emge with various doses of estrogenic hormones administered exogenously over different periods of time yielded various degrees of hyperplasia in breast tissue, mammary adenofibromas, and in the linings and glands of the genital tract. Doses of inordinate size resulted in cystic mastoplasias and genital metaplasias, but even with huge superstimulation the resultant hyperplasia of any of these tissues never approached a truly malignant state.

The author concludes that on the basis of experimental evidence, the relation of estrogenic hormones to cancer is secondary to, and strictly limited by, hereditary factors. It is entirely unlikely that the estrogenic hormones have a broader carcinogenic significance. However, as a matter of caution, it is wise to watch for unusual occurrences in man because of the comparatively short time since the introduction of estrogenic therapy.

HUGO EHRENFEST.

Sorba, M.: *Syphilis and Cancer of the Cervix*, Monatschr. f. Geburtsh. u. Gynäk. 109: 73, 1939.

In the differential diagnosis between syphilis and cancer of the cervix, errors are made because a biopsy is not done and syphilis is not thought of. Sorba's statistics revealed that among 262 cases of cancer of the uterine cervix, syphilis

malignancy, in two patients definite cervical carcinoma was found. In both patients a simple excision of the endocervix apparently effected a cure. The experiences justify the following recommendations: (1) No diagnostic curettage should be considered complete without removal and histologic examination of the cervical mucosa. After dilatation and curettage, the Hyams conization offers the simplest and safest way to accomplish this purpose. (2) Every woman past her thirtieth year should be considered a potential candidate for cervical carcinoma. It is advisable for patients in this age group to have at least one routine tissue examination of the lower half of the cervical mucosa. The only contraindication for this procedure is inflammation or tenderness in the adnexa.

Gynecologists who adopt these two recommendations, may be rewarded by the gratifying experience of recognizing and curing an occasional patient with incipient cervical carcinoma.

WM. C. HENSKE.

Aschheim, S.: Difficulties in the Histologic Diagnosis of Benign and Malignant Transformations of the Uterine Endometrium, *Rev. franç. de gynéc. et d'obst.* 33: 471, 1938.

Not infrequently histologic sections of endometrium present difficulties in determining whether or not the tissue is benign or malignant. Aschheim reviews some cases reported in the literature where a diagnosis of cancer was made and an operation performed because nodules of squamous epithelium were found in the uterine endometrium. He himself has encountered this condition nine times. Even today there is very little in the literature concerning this condition.

The squamous cells, which are found in the uterine endometrium, differ from squamous cell carcinoma in that nearly all the cells are of equal size, they are compact or separated only by a tiny space, but they have no intercellular bridges of tissue between them. Their nuclei are round or oval, they stain faintly with hematoxylin, there is no atypia, there are no giant cells, and mitoses are rare. In the author's experience there was often an edematous and leucocytic infiltration in the stroma.

The author believes that the squamous cells are the result of an irritation of the columnar cells of the endometrium. Such an irritation may be an inflammation combined with irritation due to estrogenic hormone. It is well known that squamous epithelium has been found in the uterine endometrium in the presence of gonococcal infections and also that in the rat and mouse, injections of estrogenic substance will bring about a transformation of uterine endometrium into squamous epithelium. In the treatment of these cases the decision must rest on the clinical symptoms and not only on the histologic appearances. In young women therefore therapy should be conservative and should consist of repeated curettements. Cure will follow in many cases. On the other hand, in older women if hemorrhage recurs, it is best to perform a hysterectomy.

J. P. GREENHILL.

Filkel, R. K.: The Polarigraphic Study of the Serum of Women With Carcinoma of the Genitalia, *Zentralbl. f. Gynäk.* 63: 647, 1939.

A new serologic test of carcinoma is described. It consists of a polarigraphic study of the serum. In a series of 176 cases of carcinoma, the diagnosis was correctly made in 92.6 per cent, and among 107 cases of recurrence of cancer, the incidence of correct diagnosis was 88.9 per cent. Early carcinoma could be detected in 87 per cent of the cases. However, the cancer reaction is not specific, because a positive test may be obtained in cases of pelvic inflammation. In spite of this the test proved helpful in cases of recurrence and in doubtful cases.

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of cells only, grows more quickly and succeeds in covering most of the field of the erosion. This is called the first stage of healing. Later on, the slower-growing squamous epithelium begins to creep over or under the columnar layer. This is the second stage of healing.

The therapy of the erosion therefore falls into three stages: first, the healing of the discharge; second, the combating of the inflammation; and third, the stimulating of the potential activity of the neighboring squamous epithelium by substances that support epithelial growth, such as scarlet red.

The most important lesion of the cervix is squamous cell carcinoma, which accounts for about 90 per cent of the uterine carcinomas, whereas the type arising from the glandular epithelium of the cervix represents roughly 2 per cent. The balance, 8 per cent, is accounted for by carcinoma of the endometrium.

A biologic difference between normal and carcinomatous epithelium can be utilized to establish a clinically visible difference in the two epitheliums. The normal epithelium of the cervix contains, in the superficial cell layers, large quantities of granular glycogen, which is produced and stored by the cells. Carcinomatous epithelium loses the potency to produce as well as to store glycogen and is therefore free from this substance. To differentiate the glycogen-containing and glycogen-free areas, the cervix is brought in contact with a dilute aqueous solution of iodine. The best solution has been found to be one containing 1 gm. of iodine, 2 gm. of potassium iodide and 300 c.c. of water. This solution stains the normal, glycogen-containing cervical epithelium, a dark brown, whereas carcinomatous epithelium remains pale. There are several other pathologic changes which also prevent the production and storage of glycogen. Since only a biopsy of the surface epithelium is necessary, there is no need for an exploratory excision: scraping the surface epithelium with a sharp curette is sufficient. The diagnosis can and should be made before the phase of downgrowth.

J. P. GREENHILL.

Geisendorf, W.: Some Observations on the Colposcope, *Bull. Soc. d'obst. et de gynec.* 28: 128, 1939.

Geisendorf was skeptical of the value of the colposcope until he went to visit Hinselmann. After studying the colposcope for a month he became convinced that this instrument not only permits better observations of cervicitis, vaginitis, leucorrhea, and traumatic lesions but that above all it is the only means of detecting early cancer of the cervix. Cancer of the cervix can develop only in abnormal or atypical epithelium which can be recognized with the colposcope. This instrument should not be used only in women suspected of having cancer but employed routinely in all women. The Schiller test is a valuable adjunct to colposcopy but it alone cannot reveal cancer.

In the discussion of this paper Reeb mentioned the fact that Hinselmann found cancer in 45 of 18,000 women examined by means of the colposcope. This is an incidence of 0.25 per cent. Wispe found cancer in 0.12 per cent of 4,000 women examined with the colposcope. On the other hand, V. Mickulicz examined women only by clinical means without the aid of a colposcope and in a series of 2,597 women who had absolutely no subjective symptoms, he found three cancers in the biopsies removed in the suspicious cases. Hence, his incidence of cancer was 0.115 per cent. Reeb, therefore, concludes that there is practically no difference in examining women with and without the colposcope as regards the detection of early carcinoma of the cervix. However, the clinical examination must be thorough.

J. P. GREENHILL.

Wolner, Anthony: The Early Diagnosis of Cervical Carcinoma, *Surg. Gynec. Obst.* 68: 147, 1939.

The study is based on 59 cases in which a routine removal of the cervical mucosa was done for purposes of a systematic histologic investigation. Although none of the cases revealed symptoms or clinical findings which indicated

In discussing this report, Clemmey mentions that while working in East Africa, he had seen two instances of cervical cancer with complete procidentia in native women.

HUGO EHRENFEST.

Oyarzun, Romeo Cadiz: Primary Cancer of the Vagina, *Bol. Soc. chilena de obst. y ginec.* 11: 7, 1937.

The author states that primary cancer of the vagina occurs in only 2.2 per cent of all genital cancers. Four cases are reported. The author prefers surgical treatment in Grades 1 and 2 types of cancer of the vagina.

MARIO A. CASTALLO.

Pund, Edgar, and Greenblatt, Robert: Granuloma Venereum of Cervix Uteri (Granuloma Inguinale) Simulating Carcinoma, *J. A. M. A.* 108: 1401, 1937.

A heretofore unrecognized entity, granuloma venereum of the cervix, clinically simulates carcinoma of the cervix. Since the involvement by the Donovan body occurs elsewhere than in the groin and on the external genitalia, the name of granuloma venereum is preferable. It is characterized clinically by a tuft of reddish meaty tissue, raised above the surface, clean in appearance, velvety soft and resilient to palpation, and it does not bleed readily to touch. Histopathologically, the essential features are the exuberant granulation tissue reaction in which the pathognomonic cell is found. This cell is a large mononuclear cell with intracytoplasmic spaces in which are dispersed the so-called Donovan bodies. The affinity of the intracyclic bodies for silver salts facilitates the recognition of the characteristic cell. With silver these bodies are stained black to brown and have a safety pin appearance because of their elongated ovoid outline and intense bipolar staining reaction.

GROVER LIESE.

Keller, R., and Meyer, P.: Some Considerations of Cancer of the Body of the Uterus, *Rev. franç. de gynéc. et d'obst.* 34: 149, 1939.

The authors observed 82 cases of cancer of the body of the uterus in which the diagnosis was made by means of a histologic examination of tissue obtained by curettement. Of the 82 patients, 55 were subjected to operation, 24 had radiation therapy and three were not treated. The postoperative mortality for the abdominal operation was 17.8 per cent and for the vaginal operation 3.8 per cent. The total incidence of cure for all the methods of treatment was 53.4 per cent. The patients treated by radiation alone of whom there were only 14 inoperable cases, yielded a cure rate of 35.7 per cent.

The treatment of choice in operable cases of carcinoma of the body of the uterus is operation. If the patient is in good condition, the operation should consist of total abdominal hysterectomy with removal of the adnexa. In patients with low resistance and in very old women, a vaginal hysterectomy should be performed. Inoperable cases should be treated by radiation therapy.

J. P. GREENHILL.

Handley, R. S., and Howkins, John: Sarcoma of the Uterus, *Lancet* 2: 1246, 1937.

In a study of sarcoma of the uterus 40 cases are discussed. Sarcoma represents 1 per cent of the mesodermal tumors of the uterus reviewed and 2 per cent of the malignant tumors of the uterus. Treatment advised consists of a panhysterectomy with wide excision and the simultaneous removal of both appendages. This should be followed by deep x-ray therapy in all cases. Of 25 patients operated upon more than five years ago, 4 are alive and well, and one is alive but dying of a recurrence. The frequency of mitotic figures in a tumor is found to be the most reliable factor in the diagnosis. Little correlation between histologic cell type and prognosis could be demonstrated.

CARL P. HUBER.

Leip and Otto: **Cervical Carcinoma Which Arose on 12 Year Old Leukoplakia**, Zentralbl. f. Gynäk. 61: 242, 1937.

This patient was carefully observed for twelve years, during which time she had a leucoplakia of the cervix. At the end of this time carcinoma developed on the site of the leucoplakia. This case and those reported by others support Hinselmann's contention that the average latent period for development of a carcinoma from the matrix zone is between ten and fifteen years. Hinselmann's advice to remove and examine such matrix zones should be followed.

J. P. GREENHILL.

Holtermann: **Abnormally Slow Growing Carcinoma of the Cervix**, Zentralbl. f. Gynäk. 61: 564, 1937.

The writer reports the case of a 41-year-old woman who had a carcinoma of the cervix which remained in an operable condition for twenty-one months after the first appearance of clinical symptoms and fifteen months after a histologic diagnosis was made. The patient was given radium treatment seventeen months after histologic diagnosis was made, and the uterus was then removed. The patient was alive and well more than five years after treatment was begun. The author reports two similar cases. All three patients were relatively young (34, 41, and 44), all did not have treatment for many months after the diagnosis was made (10, 15, and 15 months), and all were alive and free from recurrence since combined radium and operative therapy. Despite these exceptions, all patients with a diagnosis of carcinoma of the cervix should be treated without delay.

J. P. GREENHILL.

Todd, T. F.: **Two Cases of Carcinoma of the Cervix in Procidentia Uteri**, Proc. Roy. Soc. Med. 30: 1343, 1937.

The rarity of cervical carcinoma associated with complete prolapse of the uterus is one of the most striking contrary findings to the commonly accepted theory that chronic irritation is an important etiologic factor in the genesis of cancer. Procidentia is common, yet there are less than 40 cases of superimposed cervical cancer on record, to which the writer adds two new observations. The first case concerns a 41-year-old para vi, seen less than a year after her last full-term delivery. A vaginal panhysterectomy was done, followed by local radium application and deep x-ray therapy. She died about eleven months later with a large abdominal mass.

The second case occurred in a para ii, aged 62 years. She had the prolapse for twelve years and off and on wore a pessary. She received radium and x-rays. The local lesion disappeared within a month, and there has been no recurrence so far. (No dates are given.)

HUGO EHRENFEST.

Basden, M.: **Carcinoma of the Vagina Complicating a Complete Procidentia**, Proc. Roy. Soc. Med. 30: 1483, 1937.

By means of a vaginal hysterectomy the prolapsed uterus and vagina were removed. There was a carcinomatous ulceration on either side of the vagina. Many years ago patient had worn a ring pessary but not for the past seventeen years. She made a good recovery but refused a suggested removal of the inguinal glands. At the Marie Curie Hospital among about 1,600 cases of cancer of the female genitalia, there were several cases of complete prolapse associated with carcinoma of the fundus but only two with cervical cancer. (Cancers with slighter degrees of procidentia are not included in this figure.) It is interesting to note that in one of the two cervical cancers with complete prolapse, radium application cured not only the cancer but also the prolapse by the resulting contraction.

was 51 per cent. Radium therapy was used in 253 cases, of which 51 were operable. One of these patients died at the beginning of treatment, and 21 (42 per cent) were cured. Of the 202 inoperable cases, 21 were alive after five years, i.e. 10 per cent; the immediate mortality was 18, or 8.5 per cent. Of all patients, operable and inoperable, treated with radium 42 (16.5 per cent) were living after five years. The immediate mortality was 19 (7.5 per cent). Latterly the immediate mortality has been lessened and is now about 4 per cent for those treated with radium.

J. P. GREENHILL.

**League of Nations: Annual Report on the Results of Radiotherapy in Cancer of the Uterine Cervix, Acta. obst. et gynec. Scandinav. 18: Supplement II, 1938.**

This is the second report issued by the League of Nations and includes analyses from nine radiotherapeutic centers throughout the world (U. S. A. (2), Brussels (1), England (3), France (2), and Sweden (1)). Information was collected concerning 6,570 patients who had cancer of the cervix. Of this number 5,672 (86.2 per cent) had radiotherapy. The results after five years were as follows:

Alive without recurrence	26.3 per cent
Alive with recurrence	1.8 per cent
Died of cancer	68.8 per cent
Died of intercurrent disease	2.0 per cent
Lost sight of	1.1 per cent

The 5,672 women were grouped as follows:

Stage I	10.7 per cent
Stage II	28.7 per cent
Stage III	42.6 per cent
Stage IV	18.0 per cent
Unclassified	0.04 per cent

The results of treatment for each group was as follows:

	RELATIVE CURE RATE
Stage I	55.2 per cent
Stage II	36.3 per cent
Stage III	21.2 per cent
Stage IV	5.3 per cent
Unclassified	0.0 per cent

Total Relative Cure Rate 26.3 per cent

J. P. GREENHILL.

**Shaw, William Fletcher: Radium Versus Wertheim's Hysterectomy in the Treatment of Carcinoma of the Cervix, Surg. Gynec. Obst. 64: 332, 1937.**

It appears that we are getting at least the same percentage of cure with the use of radium as with Wertheim's operation, but with this great difference, that the radium cases include advanced as well as early ones, while the operation list necessarily includes only those in the first two stages.

Even if the results with radium were just as good as, but no better than, those with the operation, radium would be the treatment of choice. There is such a slight mortality and, what is almost of more importance, the convalescence is painless, whereas after Wertheim's operation a large percentage of the patients are very ill for some days, and at best are very slow in recovering from such a heavy strain.

WILLIAM C. HENSKE.

**Keller, R.: Drainage and Thrombosis, Bull. Soc. d'obst. et de gynéc. 26: 253, 1937.**

In a series of 60 Wertheim operations performed for carcinoma of the cervix, the author encountered only two cases of postoperative thrombosis. This is

Meigs, Joe V.: Cancer of the Ovary, *New England J. Med.* 220: 545, 1939.

On the basis of 147 cases of ovarian cancer seen in the Massachusetts General Hospital during the years 1901 to 1933, the writer discusses origin, symptomatology and diagnosis, histopathology, and treatment of these neoplasms. This analysis leads him to the following conclusions: Ovarian cancer of the solid type always is very serious. The malignant papillary cystadenoma is about as malignant as any other epithelial growth. Early diagnosis is necessary for improvement of curative results, which are unsatisfactory and worse than those obtainable in cervical or mammary carcinoma. The use of the peritonoscope should prove of great value in diagnosis. Bilateral oophorectomy with total hysterectomy is the operation to be carried out if possible. Its postoperative mortality is low. The rupture of cysts before or during operation and the use of the trocar cannot be proved dangerous by their end results, however, spilling of cyst contents always should be avoided. X-ray treatment to date has not proved of much curative value but more modern methods may still give better results. Every ovarian tumor that is removed should be opened before the surgeon ends his operation to rule out any suspicious papillary area.

HUGO EHRENFEST.

Mitra, Subodh: Carcinoma of the Cervix in India (the Five-Year End-Results), *Brit. M. J.* 1: 747, 1937.

Malignant disease of the uterus is as common in India as it is elsewhere. A follow-up of the patients is very difficult, owing to economic, civic, and other factors. The author lists statistical studies of results with different methods of treatment. The comparative figures from the literature indicate that in the hands of experts the results of radiation therapy might be as good as those of operation, but in no case will they exceed them.

Interesting tables of the author's series of cases and those of others are presented.

F. L. ADAIR AND S. PEARL.

Smith, Frank Raymond: The Effect of Fractional Roentgen Technic on the Incidence of Vaginal Fistulae in Carcinoma of the Cervix, *Radiology* 30: 748, 1938.

The incidence of vaginal fistulas in untreated cases of carcinoma of the cervix is more than twice as great as in treated patients. Vaginal fistulas are manifestations of progress of the disease rather than of injury by radiation.

A recent very low incidence of fistulas in the experience of the writer is attributed to a delay between the completion of roentgen therapy and local application of radium. At least one month should elapse between divided dose roentgen therapy and radium treatment; and at least two or three weeks when massive dosage is used.

S. D. SOULE.

Schroeder, R.: The Treatment of Cervical Carcinoma, *Zentralbl. f. Gynäk.* 61: 546, 1937.

Schröder reviews the results of treatment of cervical carcinoma during a period slightly more than ten years in the Gynecological Clinic in Kiel. He followed up 604 patients who have been treated for a period longer than five years. Of these 171 (28 per cent) were classified as cases of absolute cure. The operable cases (58 per cent) were divided into four groups, (1) early, (2) endophytic, (3) exophytic, and (4) with deeper nodules.

Operation was undertaken in 302 cases, or 50 per cent; 178 patients were treated by Wertheim's method, with a primary mortality of 18 per cent, which with Schauta's operation amounted only to 1.5 per cent. The cure rate following Wertheim's operation was 36 per cent and that following Schauta's operation



The author treated all 11 cases of visceral pain by presacral neurectomy with complete success. The somatic pain should be best relieved by intrathecal alcoholic injections or cordotomy. The lumbar puncture is ordinarily made in one of the upper lumbar spaces. The motor fibers are not equally affected.

The etiology is discussed.

It is stressed that when appropriate treatment fails to relieve pain the patient is entitled to comfort without becoming an addict to morphine. It is emphasized that there will be failure in pain relief unless the appropriate treatment is given. This necessitates an accurate diagnosis of the type of pain.

H. CLOSE HESSELTINE.

**Binet, A.: Analgesic Medication for Inoperable. Cancer of the Uterus and the Tolerance of the Organism for Morphin, Bull. Soc. d'obst. et de gynéc. 26: 341, 1937.**

In spite of the recent advances in the treatment of carcinoma of the uterus, a large proportion of women with such cancers suffer excruciating pain. The usual analgesics, such as aspirin and pyramidon, have only a momentary effect so that morphine must be used to secure any relief. Attempts are being made to avoid this by surgical, physiotherapeutic, and even biologic means, but they have not yet succeeded in replacing morphine. In a recent case of inoperable cancer Binet performed a resection of the superior hypogastric plexus with excellent results. Other operative procedures are chordotomy and lumbar ramisections. Cobra venom has also been suggested and tried by the author, but his patients did not obtain any relief from pain and cried for morphine. The chief drawback of morphine is the tolerance which patients develop. This occurs rapidly. The author reports a case where a patient gave herself 60 hypodermic injections of 0.02 cm. of morphine every day. This is the equivalent of 120 ordinary hypodermic doses of morphine.

J. P. GREENHILL.

**Curtillet, E.: The Treatment of Pain in Cancer of the Cervix, Rev. franç. de gynéc. et d'obst. 32: 306, 1937.**

The author points out that morphine is generally employed to relieve the pain which is associated with cancer of the cervix. However, it is unsatisfactory because it weakens the patient, and produces a condition of stupor, it is temporary and costly, and the patient continues to suffer more or less between injections. Another medical measure to relieve this type of pain is cobra venom, but the failures with this substance are more frequent than the successes.

Among the surgical procedures recommended to relieve this type of pain are the following:

1. Section of the posterior roots of the lumbar nerves. This operation is now seldom performed.

2. Section or resection of the sympathetics. The chief operations in this class are hypogastric periarterial sympathectomy.

3. Medullary interventions of which cordotomy is the most common. The results are not very satisfactory.

4. Injections of alcohol.

The author recommends that the first procedure to be tried is subarachnoid injection of alcohol, because it is the simplest. If this fails, the superior hypogastric plexus should be resected if the patient's condition permits. If, however, this operation cannot be done or if the pain is sacral or renal in origin, a cordotomy will have to be done.

J. P. GREENHILL.

striking because in the author's clinic there is a far greater incidence of post-operative thrombosis even after simple operations. He attributes the infrequency of this complication in his Wertheim operations to the routine use of Mickulicz drains. They drain both abdominally and vaginally and traverse the entire field of operation. They assure complete removal of all secretions from the wound and hence prevent contaminating the field of operation. Furthermore the Mickulicz drain favors adhesions between the upper end of the wound and the omentum and intestines. These adhesions permit small engorged blood vessels to grow into the operative field, and they set up an active circulation and hence prevent the venous stasis which favors thrombosis. The author does not want to conclude that every operative case should be drained, yet he calls attention to the report by Gosset in which the latter claims unusual results following drainage after all his operations for fibroids.

J. P. GREENHILL.

Holterman, C.: *Skin Metastases in Cases of Genital Carcinoma and Their Treatment*, Ztschr. f. Geburtsh. u. Gynäk. 114: 350, 1937.

The writer calls attention to a striking increase in skin metastases noticed in recent years in cases of carcinoma of the genitalia. In the Cologne University Woman's Clinic the author observed many cases of skin metastases. He believes this is due to the fact that with improved methods of treatment, patients live longer than formerly, and there is more time for the development of such metastases. The treatment is purely local. The author prefers surgery to radiation. In not a single instance where he removed the skin metastases surgically has there been a recurrence. The author, however, advocates postoperative radium treatment of the surgical scar. The prognosis of skin metastases is better than is generally supposed.

J. P. GREENHILL.

Jonsell, S.: *Observations on Vaginal Metastases in Carcinoma of the Cervix Uteri at Radiumhemmet*, Acta Radiologica 18: 607, 1937.

This study is based on 1,881 cases of cervical cancer examined at Radiumhemmet (Stockholm) from 1914 to 1930. At the first examination vaginal metastases were found in 5.3 per cent of the series. In patients already treated, they developed in 7.5 per cent. Metastases in the upper half of the vagina before treatment do not seem to impair the prognosis. Metastases in the lower parts of the vagina as a rule occur in advanced cases. Vaginal metastases in cases already radiologically treated are ominous and associated with the appearance of other recurrences. In a few cases, where vaginal metastases were the only sign of cancer, permanent healing was obtained through renewed treatment.

J. P. GREENHILL.

Todd, T. F.: *The Pathways and Relief of Pain in Advanced Carcinoma of the Cervix Uteri*, Lancet 2: 555, 1937.

Somatic and visceral are the two types of pain encountered in malignancy of the cervix. Somatic pain is prone to occur in neglected and untreated cases. It is experienced in the legs and thighs due to involvement of the afferent paths to these areas. The visceral pain is localized in the lower abdomen and pelvis, typically diffuse. Occasionally both types are observed in the same patient.

Treatment directed at symptomatic relief may be administered only after adequate evaluation. The pain must prevent sleep and the patient must be willing to undergo the procedure.

The cause must be accurately determined lest failure result. The autonomic nerve fibers are accessible in the parasympathetic plexus, while the peripheral nerves transverse the pelvis in the femoral, genitofemoral, lateral cutaneous, obturator, fifth lumbar, sacral, pudic, and coccygeal nerves.

- New England Obstetrical and Gynecological Society.** *President*, Thomas Almy. *Secretary*, R. J. Heffernan, 475 Commonwealth Avenue, Boston, Mass. May and December.
- Pacific Coast Obstetrical and Gynecological Society.** *President*, Alice F. Maxwell. *President-Elect*, John Vruwink. Meetings held in late fall or early winter, rotating in the larger cities of the Pacific Coast. . .
- Washington Gynecological Society.** *President*, H. P. Ramsey. *Secretary*, James R. Costello, 900 17th Street, N. W., Washington, D. C. Fourth Saturday, October to May.
- New Orleans Obstetrical and Gynecological Society.** *President*, H. C. McGee. *Secretary*, H. W. Reddock, 1430 Tulane Avenue, New Orleans, La. Meetings held every other month.
- St. Louis Gynecological Society.** *President*, Percy H. Swahlen. *Secretary*, Joseph A. Hardy, Jr., 3720 Washington Blvd. Second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** *President*, T. Floyd Bell. *Secretary*, R. Glenn Craig, 490 Post Street, San Francisco, Calif. Regular meetings held second Friday in month, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.

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## Item

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### American Board of Obstetrics and Gynecology

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting in Atlantic City, N. J., on June 8, 9, 10, and 11, 1940, immediately prior to the annual meeting of the American Medical Association in New York City.

Application for admission to Group A, Part II, examinations must be on file in the Secretary's Office not later than March 15, 1940. Formal notice of the time and place of these examinations will be sent each candidate several weeks in advance of the examination dates. Group A, Part II, candidates will be examined on June 8 and 9, and Group B, Part II, on June 10 and 11, 1940.

The annual dinner of the Board will be held in New York City on Wednesday evening, June 12, 1940, at the Hotel McAlpin.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh, (6) Pa.

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## Erratum

In the article by Dr. Theodore Neustaedter, "The Effect of Ingested Estrone (Progynon DH) and Parenterally Administered Synthetic Progestin (Proluton) Upon the Human Castrate Uterus," page 609, October, 1939 issue, the title should read: "The Effect of Ingested Alpha Estradiol . . ." instead of "The Effect of Ingested Estrone. . . ."

## ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES\*

(*Appears in January, April, July, October*)

- American Gynecological Society.** *President*, F. L. Adair. *Secretary*, Richard W. TeLinde, 11 East Chase Street, Baltimore, Md. Next meeting, June 17-19, 1940, at the Seignory Club, Quebec, Canada.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** *President*, James R. McCord. *Secretary*, James R. Bloss, 418 11th Street, Huntington, W. Va. Next meeting, September 19 to 21, 1940, Excelsior Springs, Mo.
- Central Association of Obstetricians and Gynecologists.** *President*, Ralph A. Reis. *Secretary-Treasurer*, W. F. Mengert, Iowa City, Iowa. Annual meeting, Indianapolis, Ind., October, 1940.
- South Atlantic Association of Obstetricians and Gynecologists.** *President*, Robert E. Seibels. *Secretary*, Robert A. Ross, Durham, N. C. Next meeting, February 9 to 10, 1940, Richmond, Va.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, Ludwig A. Emge. *Secretary*, Norman F. Miller, Ann Arbor, Mich. Next meeting, June, 1940, New York City.
- New York Obstetrical Society.** *President*, William S. Smith. *Secretary*, Henry T. Burns, 162 East 71st St., New York City. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** *President*, Thomas B. Lee. *Secretary*, John C. Hirst, 500 North 20th St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** *President*, Julius E. Lackner. *Secretary*, Edward Allen, 55 East Washington St., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** *President*, Goerge H. Davis. *Secretary*, Bruce A. Harris, 175 Clinton St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Avenue.
- Baltimore Obstetrical and Gynecological Society.** *President*, J. J. Eastman. *Secretary*, Frank K. Morris, 11 East Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Building.
- Cincinnati Obstetrical Society.** *President*, E. W. Enz. *Secretary*, Edward Friedman, 19 West Seventh St., Cincinnati, O. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Esther C. Wallner. *Secretary*, Samuel S. Gordon, 520 Heyburn Building, Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Howard Stearns. *Secretary*, William M. Wilson, 545 Medical Arts Bldg., Portland, Ore. Last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** *President*, S. A. Chalfant. *Secretary*, Dr. Joseph A. Hepp, 121 University Place, Pittsburgh, Pa.
- Obstetrical Society of Boston.** *President*, Raymond S. Titus. *Secretary*, Judson A. Smith, 262 Beacon St., Boston, Mass. Third Tuesday, October to March, Harvard Club.

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\*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL.

"Home is the palace of the husband and father. He is the monarch of that little empire, wearing a crown that is the gift of heaven, swaying a sceptre put into his hands by the Father of All, acknowledging no superior and fearing no rival." And this less than one hundred years ago! Even in the scriptures these views found support. Every woman today must regard with contempt the opinions the Apostle Paul expressed in his epistles concerning the place of woman. There was also a basic human principle involved in this position of woman. It is inherent in mankind for the stronger groups to attempt to subjugate the weaker. This is evident today in this troubled world of ours. The fact that woman is physically weaker than man, in part, accounts for man's attempt to dominate her. Moreover, this very weakness made it necessary in the past for her to look to him, the stronger, for protection. The matter of education also played its part. Only a few centuries ago, learning was reserved for men, and women were accorded a scant share in what education there was to be had. As men became wiser, it afforded them further excuse for assuming the ascendancy.

Today in all advanced civilizations, woman has succeeded in emancipating herself from the position she has occupied in the past. She is respected; she has acquired the same social, economic, and political privileges as men; she is protected by the laws and ethics of the community in which she lives; she is the equal of man in all respects except one—she is still, and always will be, the weaker physically. This physical difference will always exist, for her endocrine glands design and determine her physical characteristics. This lack of physical equality, however, today is unimportant, for physical strength is neither necessary for her protection, nor essential in her acquiring the means for her support.

But granting that all that has been said is true, and that woman has attained equality with man, we still have to recognize another great difference, a difference that may be found to lie in the mental approach of woman to the problems of life, and the reactions she exhibits in her contacts with others. Nineteen years ago, I presented a paper before this Association in an attempt to account for the physical and mental differences between man and woman. It was based upon the then meager knowledge of the endocrine system. Much said at that time was frankly admitted to be theory, but inasmuch as some of those theories have since become established facts, one may speak with more assurance upon the subject we are to discuss today.

Human beings, as well as lower animals, are still activated, and their behavior influenced, by the struggle for self-preservation and the urge to reproduce. With the ramifying interests and complexities of our civilization, often it may be difficult to recognize the influence that these fundamental laws play in our lives.

In the human family, as well as in most animals, the burden of reproduction is entirely borne by the female. From puberty through the menopause, woman is under the domination of her reproductive glands. For about thirty years of her life, conditions are reproduced each month that make possible the implantation and development of a fertilized

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American Association of Obstetricians, Gynecologists and  
Abdominal Surgeons

Fifty-Second Annual Meeting, September 7, 8, and 9, 1939

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## PRESIDENTIAL ADDRESS\*

JAMES E. KING, M.D., BUFFALO, N. Y.

I DESIRE first to express to the members of this Association my heartfelt appreciation for the honor conferred upon me in electing me President. Those of you who have occupied this chair will understand my feelings, and the younger members no doubt cherish the hope that they one day will have this experience.

In my address, I regret that I cannot bring you any new scientific truths. It would seem, however, that there is no subject which should have greater interest for this Association than a discourse on woman, herself. Not a discussion on her beauty or her diseases, for those we know, but rather to attempt to account by fact and fancy for her peculiarities and to explain her inconsistencies, and those delightful surprises we so often experience in our contacts with them.

Woman for centuries has been the slave of man. In China and India, the majority of women may still be regarded as slaves. It is only in the past one hundred years, and in those countries most highly civilized, that woman, by persistent effort, has succeeded in securing for herself the economic and political rights so long enjoyed by man. Occasionally before the nineteenth century, some lone woman's voice was heard in protest. In 1638 Anne Hutchinson was excommunicated and banished from the Massachusetts Colony because she had criticized the men in authority and had dared to preach. It was said that she had spoken "with the impudent boldness of a proud dame." Even in 1844, the Reverend Danforth reflected the views of his day when he wrote,

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\*Given at the Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 7 to 9, 1939.

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NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

to its simplest terms, love may be regarded as the intellectual refinement of the impulses springing from gonadal secretion. Prompted by their gonads, Leanders have performed deeds of valor and faced the greatest perils. Their secretion has inspired the most noble acts as well as instigated the most sordid crimes. Surely here we cannot question the influence of the ductless glands upon mental attitudes and behavior.

In our civilization when a girl reaches the age of fourteen years, it is a time when those interested watch her with care, marveling at the physical changes that so rapidly take place, and at the still more astounding changes that occur in her mental reactions. The girl herself notes with wonder the enlargement of her breasts, the filling out of her body and other more or less definite changes that characterize her approach to womanhood. The fear or surprise that her first menstruation may cause depends upon how well she has been prepared to expect it. From this moment it would appear that she, like Mother Eve, had eaten of the fruit of the Tree of Knowledge and had thereby become sex conscious. There is developed in her that attribute, enhanced by Victorian influence, which we term modesty. She lays aside her childish views and begins to think and act as a woman. These manifestations may be observed by all, but the physician can visualize the changes that are taking place in her reproductive organs, and the complex readjustment of her glandular system necessary to bring them about. Thirty years ago, these evidences of puberty were believed to be due simply to an awakened activity of the gonads. It is now known that they occur through the interrelated action of various glands. The part played by some can as yet be explained only by theory. The thymus body, the so-called childhood gland, is one of these. Until puberty is well established, it is large, but following the first changes of puberty, it rapidly atrophies. The theoretical interpretation for this is that, its life span being fourteen years, it exerts during that time an inhibitory action upon the gonadotropic principles of the anterior pituitary. With the atrophy of the thymus, the pituitary is freed to establish the menstrual cycle. The pineal gland is also regarded as a gland of childhood, but little is as yet known of it except what is suggested by the occasional tumor which inaugurates a precocious sex development in the male.

With the complex physical phenomena that result from the secretion of the temporary glands with that of the permanent glands concerned in menstruation, it is not surprising that there also may be associated certain mental reactions during the menstrual cycle. Women so frequently experience a mental depression at those times, that slight degrees may be regarded as normal. The thyroid plays an important role in menstruation. It is observed occasionally to become temporarily enlarged. This may result in an effort of the thyroid to supply additional secretion demanded at menstruation. If the threshold can be raised to meet those requirements, no mental depression occurs. All degrees of this depression may be encountered. In some women the depression experienced may constitute a real dread of menstruation. Krugelstein has stated that in 107 instances of suicide observed by him in women in the reproductive age, all were menstruating at the time.

ovum. The secretion of her anterior pituitary causes to develop during each menstrual cycle, two temporary glands, the Graafian follicle and the corpus luteum. Should pregnancy occur, in addition to the physical changes that take place, there is a readjustment of her thyroid and pituitary, and the placenta itself, as it develops, becomes an important endocrine gland. Following the birth, another readjustment takes place, with lactation and the involution of her reproductive organs. At the age of approximately forty-five, the menopause occurs, and a marked change ensues in the physiology of her endocrine system, with frequent maladjustments that cause the discomforts from which many women suffer. The part that man plays in reproduction is simple and untended by consequences to himself. His reproductive powers are not limited to any definite period, but they gradually wane and finally cease at an age that varies in different individuals. But for thirty years the potent chemicals secreted by her reproductive glands hold woman under constant control.

There are a number of well-recognized facts known today concerning the endocrine glands that have a bearing on this discussion. The first is that among these glands there exists a definite interdependence, and upon the normal function of each depends the normal function of one or more of the others; second, the evidence of this relationship may be seen as an inhibition, a stimulation, or as a control of normal secretion; third, that certain of the glands have a definite individual span of life, at the end of which their function ceases, a function which may extend from a few days to a few years; fourth, that the secretions consist of extremely potent chemicals and minute quantities of these enter the blood stream and are thus carried to the other ductless glands; fifth, that various glands may secrete a substance similar in its effect to that of certain of the others; and sixth, that these glands are subject to hyperplasia of the secreting cells, which is reflected in a hyperfunction, or if an atrophy of the secretory cells occurs, a hypofunction results.

It is generally conceded that physical characteristics are dependent upon the normal secretion of the endocrine system. It is also true that many of our mental characteristics depend upon the secretion of these glands, and the dominance of certain glands in an individual will determine the outstanding features of his personality. Heredity is, therefore, believed to play a part in the development of the endocrine system, and at times it appears as though this were true.

It is not difficult to believe that the potent chemicals, thrown into the blood stream by the glands, may react to develop our mental states and to influence our thought and action. That chemicals in the blood will determine thought and action is apparent in the effects produced by cocaine, morphine, alcohol, and cannabis indica.

We find sex attraction in the human family variously modified by custom and the influences which are the result of intelligence and education. Through intelligence man is able to evaluate qualities of mind in another, and this spiritual attraction, combined in varying degrees with sex attraction, constitutes the emotion called "love." Reduced



of the enlarged pituitary. It is possible that these pregnancy cells are the specific cells that secrete this hormone. With the development of the mother instinct in animals, there may be observed changes affecting their disposition. In their unreasoning desire to protect their young, even domesticated animals may become ugly, clawing, or snapping at any who attempt to handle them or their newborn. This cannot be the result of even the most rudimentary mental process. These protective reactions are in some manner connected with the adrenals. The law of self-preservation is obviously dependent largely upon the adrenals, in both the need for unusual strength often required and a fierceness that may be displayed when necessary. It would seem possible that these glands by their secretion arouse the protective fierceness observed in these mothers.

As to the liberation of the lactogen which stimulates lactation and mother love, there is yet no definite laboratory proof. It is known, however, that the progesterone of the corpus luteum early stimulates the development of the mammary glands, and as the placenta develops, the progesterone it produces carries on the work of the atrophying corpus luteum. This placental hormone apparently not only inhibits lactation, but also holds in check the posterior pituitary. The onset of labor can reasonably be assumed to take place when the life of the placenta is brought to its close at the end of nine months. The pituitary secretion is then liberated and enters the circulation to produce contractions of a possibly sensitized uterine muscle. This is as yet pure theory, but there are the most convincing reasons for believing that the life of every placenta is definitely fixed in the various species, its span varying from twenty days in the mouse to twenty months in the elephant.

If further proof is required as to the life of the placenta, it can be found in abdominal pregnancies that go to term. At the end of nine months, the so-called spurious labor occurs. Following this the uterine contractions cease. The fetal heart sounds are no longer heard. The child is dead.

The cause of eclampsia is not known. Some day probably it will be found to be due to a dysfunction of a placenta whose perverted secretion becomes a potent poison that damages kidneys and liver, and thus, either primarily or secondarily, causes the convulsions.

It is a rather curious fact that up to about five years ago, the placenta as a ductless gland was generally neglected. This may possibly be explained by the fact that as yet no definite cells have been found which indicate that they are secretory. From the experiments of a number of investigators, however, it is now believed that progesterone is a definite placental secretion, and there is suggestive evidence that an estrogenic substance is also formed. The Langhans' cells may possibly be responsible for these secretions. It is certain that, as yet, there is nothing known of them.

In the protective care shown by birds and domestic fowl, a placenta and lactation obviously play no part. There is, nevertheless, good reason to believe that the pituitary assumes a major role, for it is

Other types of mental disturbance may also be seen. One that is relatively common is varying degrees of unreasonableness. Some women become unreasonable to a point where every remark and act is construed in a manner to awaken self-pity and a sense of injustice. At times even physical violence is attempted. Women who may be lovable and sweet-tempered at other times, during menstruation become termites. Entire households may look forward to the approaching period with as great dread as the women themselves. Another not uncommon manifestation is expressed in the impulse to work. Women so affected become restless, quick-tempered, and exacting in their requirements of others. They, themselves, will work at tasks which at other times they would scorn to do, or they may be possessed by a frenzy to rearrange their household effects. The slightest criticism will produce a flood of angry tears. These latter manifestations may be regarded as due to the drive and urge of an adrenal imbalance. Just how this maladjustment is brought about is not as yet understood. That it is due to a hyperadrenalism, there is scarcely a doubt. Havelock Ellis states that Lombroso found that of eighty women arrested for opposition to the police or for assault upon others, all but nine were menstruating at the time. There is more than a suspicion that adrenal dysfunction accounts also for these physical outbursts.

There are many mental reactions in connection with pregnancy that are extremely interesting, but because of our familiarity with them, they are accepted without thought as to their cause and significance. In connection with the reactions to pregnancy, however, one must be ever mindful of the modifications that may be the result of custom, necessity and economic condition of the individual or group. It is in animals only that uninhibited reactions are seen, except in women whose status and environment are such that a placid frame of mind renders possible an unstrained response to their condition.

Women frequently express a desire for children. This is due to a natural affection for the young, that is frequently shared by the husband. This is not contingent, therefore, upon an endocrine influence, but upon a memory that possibly recalls the happiness of early motherhood and a mentality that makes it possible to hope that this experience may be repeated. In women, a welcomed pregnancy brings happiness, while one that for various reasons may not be desired will bring great unhappiness.

There is no reason to believe that in animals during gestation there is any mental response. Directly following the birth, however, mother love appears. Nineteen years ago, I suggested that this developed as a result of an internal secretion and expressed the belief that it sprang from the pituitary gland. This has recently been proved to be so, and the lactogenic hormone of the pituitary has been found to cause the expression of mother love. If other evidence is necessary, there is the fact that in animals, as lactation ceases, the protective care devoted to the young will also cease. In all animals and in women during pregnancy, the so-called "pregnancy cells" of the pituitary develop. Impaired vision and headache may sometimes result from the pressure

study. However, two glands, the thyroid and adrenals, stand out prominently. The various degrees of depression and the usual increase in weight observed at the menopause are often associated with the lesser states of hypothyroidism. The hot flushes and other indications of a disturbed sympathetic nervous system present good reasons for associating them with the adrenals. Whether these phenomena are due to uncontrolled sympathetic nerves that affect at random the vasomotor system, or whether the sympathetics act directly upon the adrenals to produce them is not known. The fact that all these symptoms can be relieved by administering the estrogenic hormone indicates beyond question that the cause is its abrupt withdrawal.

Woman is definitely a reproductive machine. What she has accomplished against great odds in raising herself from slavery to her present position, must inspire in all the greatest admiration. She has brought this about despite the many and frequent readjustments of her endocrine secretions, and the effects they produce in her mental reactions and behavior.

Woman also has acquired prominence in science and in purely intellectual pursuits; again in spite of her active glandular system. While for these achievements we admire and respect her, we love her for herself alone. It is man's conceit that prompts him at times to feel a supremacy. It is woman who actuates man to the accomplishment of his noblest ambitions. She is the inspiration for all his great and good achievements. He labors for her; he serves her; he is her slave. He is enthralled by the sublime heights to which her virtues may raise her and at times sorely shocked at the iniquitous depths to which she may sink. She has been the enigma of all ages, a creature swayed by moods and impulses. Neither the imagination of the poet nor the wisdom of the philosopher has solved her. But the solution is now at hand; it lies in those complex and potent chemicals, the secretions of her endocrine glands.

As one contemplates the changes which have taken place in woman's estate in the past one hundred years, and considers the economic importance which today she often assumes in supporting a husband and home, one may well wonder what her position will be in the next one hundred years. Will she, as some timid souls fear, mentally and physically dominate and enslave us as we in the past enslaved her? Probably not; so long as she is controlled by her reproductive glands, she will remain basically the same loveable and gracious homemaker. Yet one is occasionally half persuaded to agree with Tom Moore for:

"Disguise our bondage as we will,  
'Tis woman, woman rules us still."

known that this gland does show definite changes during the brooding season. The hen becomes possessed by a desire to set. This desire is not prompted through a mental process, but results from the secretion of the pituitary that compels her to react in this manner. It is well recognized how difficult it is to change her purpose, and many are the rough and ready methods employed to discourage her. She will set upon anything that will pass as an excuse for an egg, and at times she will even dispense with an excuse. If, however, she does set on eggs that in due time hatch, she at once assumes a proud and protective attitude in caring for her chicks that is in every way comparable to the mother love shown by animals. The hen is a timorous bird, but in the face of a danger threatening her brood, she will display great courage in their defense. Indeed, in the protection of her chicks, she is possessed of a far greater courage than she would show at any other time, when, if a similar danger threatened her life, she would flee. The most ardent admirer of the hen would not consider her intelligent. This protective care and courage must be regarded as due to a mechanistic reaction produced by the chemicals secreted by her endocrine glands.

A mental state in women that is more or less comparable to the absorbing desire of the hen to set, is seen occasionally in those who become possessed of a belief that they are pregnant. Any woman may believe she is pregnant, but the assurance of her physician to the contrary is sufficient to convince her that she is not. There are some women, however, who may present evidence of Froelich's syndrome and in whom the belief that they are pregnant becomes an obsession. These women have infrequent menstrual flow or amenorrhea, and they will rehearse their symptoms to indicate pregnancy and evince implicit faith in them. No opinion of their physician or specialist will dispel that belief. Nothing will persuade them that they are not pregnant. They proceed with their preparation; the nurse is engaged, and in one instance the woman had convinced her physician. At the expected time of labor, the nurse and physician were summoned, and her conviction was shattered only by the fact that no baby was forthcoming. With the other evidences of pituitary dysfunction in such women, it is perfectly possible that this unreasoning belief in pregnancy is due to pituitary dysfunction.

During the menopause almost all nervous disturbances or other manifestations that may occur are attributed by the laity, often quite correctly, to "the change of life." Personally, I like that phrase "the change of life," as it expresses in simple English and so perfectly what has taken place. For the physician it signifies that the ovaries have run their span of life and their function has been brought to a close. For many years the phenomena observed during this time were attributed to simple withdrawal of ovarian secretion. Today, while withdrawal of ovarian secretion is still recognized as the underlying cause, the manifestations are now known to be the result of maladjustment of other glands. The clinical evidences of the menopause are well known but the glands that produce them still offer a wide field for

the three lobes be included, it is obvious that the number of true pituitary hormones must be very limited. This being the case, it follows that each true hormone most likely has several different physiologic effects. The following list represents some of the more important physiologic effects of anterior lobe extracts which are well authenticated: (1) Specific stimulation of general body growth. (2) A thyreotropic action. (3) A gonadotrophic action. (4) A corticotrophic action. (5) A mammary secretagogue action, or prolactin effect. (6) A diabetogenic effect. (7) A ketogenic effect. (8) An increase in liver fat. (9) A lowering of respiratory quotient. (10) Change in blood lipoids. (11) Increasing oxygen consumption in thyroidectomized animals. (12) Inhibition of insulin hypoglycemia. (13) Inhibition of adrenalin hyperglycemia. (14) Retention and increase of carbohydrate stores; glycotrophic or glycostatic effect. (15) Chromatophore- and erythrophore-expanding effects.

While there is this formidable array of proved physiologic effects of anterior lobe extracts, one must agree with Carlson<sup>4</sup> who recently stated: "Many of the pituitary gland products, fractionated by modern biochemical methods and demonstrated to have physiologic and pharmacologic actions, have not as yet been shown to be true pituitary hormones—that is, to be secreted into the body fluids by this gland in health or disease." With further reference to pituitary extracts in the clinical field, Carlson added: "The least encouraging situation today is the clinical application of laboratory findings in the pituitary field. These findings have improved our diagnosis of pituitary diseases in man, but have added little to their control. At least we have not scored a success in pituitary therapy comparable to that in thyroid, pancreas and parathyroid disorders." These remarks of Carlson were made in 1936 but in general they are equally pertinent today. I realize that I am addressing an audience essentially of clinicians and if at the outset I appear to adopt a note of pessimism as regards the practical clinical application of laboratory findings in anterior lobe physiology, I do not wish by so doing to have you infer that I think that the situation is hopeless. I have, in fact, great confidence that many things of great practical value will ultimately emerge when we know more about the basic nature of pituitary disease in the human subject.

Although information of the greatest value has been obtained by the so-called chemical dissection of anterior lobe tissue into different fractions, each with its own physiologic and pharmacologic properties, it must be remembered always that the intact normal gland is functioning as a whole in the closest relationship and coordination with the nervous system and numerous other glands of the endocrine chain. This being the case, is it any wonder that the practical application of the known facts of anterior pituitary physiology has been very slow in its development?

As a result of a considerable experience, extending now over some years, in the preparation and testing of various anterior lobe extracts and of determining the effects upon extracts and their physiologic

# THE PHYSIOLOGY OF THE ANTERIOR PITUITARY AND A NOTE ON THE MEDULLOTROPHIC HORMONE\*

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I HAVE chosen as the subject for this oration, "the physiology of the anterior pituitary." The subject itself is so large that it will be quite impossible, in the course of one short address, to do more than scant justice to it. Van Dyke,<sup>1</sup> in 1936, published an excellent critical review on the physiology and pharmacology of the pituitary. This was based upon some 5,000 original articles touching upon this subject and this year this same author published a companion volume<sup>2</sup> on the same topic in order to bring his review of the current literature up to date. As these most excellent reviews of Van Dyke, as well as those of others,<sup>3</sup> are readily available, and also due to the hopeless nature of the task of adequately reviewing the literature in one lecture, I have decided that I can do best by discussing for the most part certain points in which I have special interest and which I hope may be of interest to you.

As a result of the pioneer work of such men as Horsley, Cushing, Aschner, Evans, Smith, Riddle and others, great advances have been made in our knowledge during recent years of the functions of the pituitary gland. There still remains, however, much investigational work to be done before we have a complete picture of the full significance and properties of this particularly wonderful gland. The great acceleration in the pace at which new information has been obtained relative to anterior pituitary functions has in a large measure been due to the greatly increased availability to laboratory workers of hypophysectomized animals, and here the work of P. E. Smith, Van Dyke, and Selye has been of great value.

Many individual laboratories throughout the world have each contributed to the development and unfolding of the many intricate problems relating to the physiology of the anterior lobe, and perhaps, in this, there has been no better illustration in the prosecution of scientific studies of the value of teamwork than has been seen here. This teamwork has been evidenced not only in individual laboratories but between different laboratories, both of the same institution and also of other institutions, and one might add that this cooperative effort has known no international boundaries.

One of the most perplexing problems confronting almost all workers in this field has been the multitudinous number of clear-cut physiologic effects of carefully prepared anterior lobe extracts. Since the number of cell types in the pituitary is definitely limited, even though

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## CERTAIN ANTERIOR LOBE PRINCIPLES OBTAINABLE IN EXTRACTS

*The Growth Hormone.—General Considerations:* The term growth or somatotrophic hormone refers to that phase of anterior lobe activity having to do with growth in the sense of increasing size rather than the differentiation of bodily tissue in general. The term is somewhat a misnomer since other phases of anterior lobe activity also have to do with growth. Thus each of the gonadotrophic, thyrotrophic and corticotrophic substances has a specific growth effect upon the respective target organ. It must be assumed that this hormone, as well as other pituitary hormones, is not absolutely essential to life since completely hypophysectomized animals may live for many months; but growth, except in the case of the animal hypophysectomized while still immature, does not take place.<sup>5</sup> Although no increase in bodily size occurs in the untreated hypophysectomized animal, there is plenty of evidence that the cells of individual organs can multiply and be replaced by new ones. Compensatory hypertrophy of the remaining kidney occurs after unilateral nephrectomy. The proliferation of fibroblasts and epithelial cells in wound healing is not seriously interfered with by hypophysectomy.<sup>6</sup> Numerous mitotic figures have been seen in the mammary gland of hypophysectomized pregnant rats at the time of parturition.<sup>7</sup> Transplanted tumors grow in hypophysectomized rats, though less rapidly than in normals.<sup>8</sup> Growth of various organs may therefore be largely independent of the pituitary growth hormone and the function of the latter would seem to be the regulation of the increase in the size of the body as a whole with a harmonious and proportional increase in the size of all the organs.

Since no absolutely pure growth hormone either in the chemical or the physiologic sense has been obtained, it is difficult to decide just what physiologic effects are related to this substance and not to any other. One of the difficulties here is the great variation in the threshold dose of the different anterior lobe principles. Thus the threshold for growth in the hypophysectomized rat is extremely low. A purified growth extract may cause growth when administered daily in as small an individual dose as  $\frac{1}{500}$  c.c. of an extract, 1 c.c. of which represents 1 gm. of fresh anterior pituitary substance. Such animals show no evidence of stimulation of the thyroid, suprarenals, or gonads. A much larger dose, however, may result in repair of the cortex of the suprarenal but yet have no effect upon the thyroid or gonad. The same extract, tested in adequate dosage upon the pigeon, usually shows a definite prolactin effect. Unless these important differences in the threshold dose for different physiologic responses are taken into account, one is likely to be led astray as regards the purity of any one extract.

A great deal of emphasis can be placed upon the fact that the ratio between certain different types of physiologic activity may be made to vary considerably by varying the method of extraction and processing of extracts, and thus a basis for argument can be had that each of these effects is due to a separate hormone.<sup>9</sup>

properties of varying physical and chemical procedures, I have come to the conclusion, like some others, that the number of true anterior lobe hormones must be very small, and thus in keeping with the anatomic nature of the factory which produces them. It is my opinion, for the moment at least, that all of the physiologic activities of the anterior lobe are represented by different groupings in two or three protein substances secreted by the gland. Granted that each specific effect of anterior lobe extracts is due to a specific group in a protein molecule, which molecule also contains other physiologically active groups, it would be possible to visualize the act of secretion of the normal gland in situ in one of two ways. Either the individual physiologically active groups may be liberated by some hydrolytic process, probably enzymatic, from the native protein carrier, or else the secretion consists of native proteins, each carrying many active groups. For example, in the former case one could visualize relatively small molecules representing the corticotrophic substance being set free in the circulation and being picked up and acting upon the cells of the adrenal cortex; in the latter case one would infer that different peripheral structures are acted upon by different groups in the hormone molecule, a specific group having always a specific physiologic effect.

As more is learned in the future about the basic facts of the normal secretory activity of the anterior lobe and of the manner in which this may be influenced by specific changes in the environment, external or internal, the nearer will approach the time of more rational therapeutic control of pituitary disease. Already, through the study of the effects of the products, both natural and synthetic, of other glands upon anterior lobe function and structure, very valuable therapeutic leads seem to be emerging. But here, as elsewhere in the endocrine field, the question of species variation must be considered. No matter how clear-cut the effects of certain hormone treatment of certain animals may be, there can be no certainty that the human individual will show the same response until an experimental study along similar lines on the human subject has given a positive answer. I have often wondered whether clinicians as a whole realize that in introducing any hormone preparation into the human subject they may be influencing not only the specific function for which the particular hormone is given but in general perhaps several endocrine glands other than the one which is presumably hypofunctional and on account of which the specific treatment has been administered. The results of such influence of an administered hormone upon the endocrine system in general may, it is true, be very desirable, but on the other hand this may not be the case. I have raised this point for the sole purpose of re-emphasizing the fact that the endocrine system acts as a whole and that disease of any one gland can each equally well produce repercussions in any part or all of the remainder of the endocrine system. Since the pituitary is now well established as the master endocrine gland, recognition of this general principle should always be uppermost in the mind of the clinician when called upon to treat pituitary disease by therapeutic measures.



If the new method of assay of the growth principle developed by Freud and others proves as satisfactory in the hands of others as it has in theirs, it will represent a great advance in the matter of standardizing preparations for clinical use.

*The Thyrotrophic Hormone.*—The interrelationship between the pituitary and the thyroid was first suggested by Rogowitsch<sup>16</sup> who noted enlargement of the pituitary of dogs and rabbits following thyroidectomy. Adler<sup>17</sup> discovered that cauterization of the hypophyseal anlage in larval amphibia prolonged the larval state. Coincident with this, Gudernatsch<sup>18</sup> found that precocious metamorphosis was induced in tadpoles by thyroid feeding. Allen,<sup>19</sup> using the Adler technique for removal of the pituitary, showed that the delayed metamorphosis of hypophysectomized tadpoles was associated with scanty deposition of colloid in the thyroid. The Smiths<sup>20</sup> reported that the thyroid of hypophysectomized tadpoles became extremely atrophic and that repair of the thyroid could be brought about by homotransplants of pituitary or by intraperitoneal injections of extracts of bovine anterior pituitary. Spaul<sup>21</sup> produced hypertrophy of the thyroid and acceleration of metamorphosis by injections of anterior pituitary substance. Uhlenhuth and Schwartzbach<sup>22</sup> showed that salamander larvae injected with anterior pituitary extracts consumed 40 per cent more oxygen than normal larvae. The classic work of P. E. Smith<sup>23</sup> on hypophysectomy of the rat established quite conclusively that the thyroid is dependent on the stimulating action of the pituitary; associated with the atrophy of the thyroid of the hypophysectomized rat, Foster and Smith<sup>24</sup> found that the metabolic rate was decreased as much as 35 per cent.

A close relationship between the pituitary and the thyroid has been demonstrated clinically. Cushing<sup>25</sup> stated that patients with hypopituitary conditions tend to have a subnormal metabolism. Loeb and Bassett<sup>26</sup> and Aron<sup>27</sup> produced hyperplasia of the thyroid of the guinea pig. Numerous workers have reported on the production of hyperplasia of the thyroid in a variety of laboratory animals: Janssen and Loeser,<sup>28</sup> Watrin and Florentin,<sup>29</sup> Grab,<sup>30</sup> and Junkmann and Schoeller<sup>31</sup> in the guinea pig; Benedict, Putnam and Teel,<sup>32</sup> Houssay, Biasotti and Magdalena,<sup>33</sup> and Schlittenhelm and Eisler<sup>34</sup> in the dog; Baumann and Marine<sup>35</sup> in the rabbit; Riddle and Polhemus<sup>36</sup> in the pigeon; Noether<sup>37</sup> in the hen; Schockaert<sup>38</sup> in the duck; and Anderson and Collip<sup>39</sup> in the rat.

Hyperplasia of the thyroid of the guinea pig has been demonstrated in vitro with the thyrotrophic hormone by Eitel, Krebs and Loeser,<sup>40</sup> while Houssay, Biasotti and Magdalena<sup>33</sup> and Marine and Rosen<sup>41</sup> produced hyperplasia in homotransplants and autotransplants of thyroid tissue in animals injected with anterior lobe extracts.

The administration of adequate amounts of the thyrotrophic hormone to normal animals results in the course of a few days in enlargement and hyperplasia of the thyroid. There is an increase in the metabolic rate (Siebert and Smith,<sup>42</sup> Verzar and Wahl<sup>43</sup>), increase in the heart rate (Schlittenhelm and Eisler<sup>44</sup>), exophthalmos (Schockaert,<sup>38</sup> Loeb and Friedman<sup>45</sup>), a reduction of the iodine content of the gland (Loeser,<sup>46</sup> Schockaert and Foster<sup>47</sup>), and an increase in the alcohol-insoluble iodine of the blood (Closs, Loeb and MacKay,<sup>48</sup> Grab,<sup>49</sup> Schlittenhelm and Eisler<sup>44</sup>).

The increase in metabolism resulting from treatment of normal animals with the thyrotrophic hormone is not large as a rule. Anderson and Collip<sup>50</sup> reported an average increase of 26 per cent in a large group, whereas in goitrous rats similarly treated, increases in metabolic rate as high as 162 per cent of normal were seen. These animals showed marked signs of hyperthyroidism, irritability, weakness, exophthalmos, and excessive sweating.

Hypophysectomized rats show a decline in metabolic rate to an average value about 74 per cent of normal. The thyroid glands decrease in size and the cellular elements show marked involution. The metabolic rate, the size and structure of the thyroid of these animals can be restored to normal by adequate treatment with thyrotrophic extracts.

The anterior lobe appears to have a two-fold action upon the thyroid: one to influence the rate of discharge of secretion, the other to change the morphologic structure of the gland. It is doubtful, as assay studies show, whether the mechanism involved in each case is the same.

It is possible that the thyrotrophic substance has effects other than those upon the thyroid gland. Marine and Rosen<sup>41</sup> have produced exophthalmos in thyroid-

*The Functions of the Growth Hormone.*—The general control of orderly bodily growth is probably the chief function of the growth principle. The profound effect upon skeletal structures, particularly the cranium, of hypophysectomy and the correction of such by extracts of anterior lobe rich in the growth hormone illustrate in a very striking manner the physiologic significance of growth hormone activity. While it probably has little effect upon differentiation of the soft tissues, the recent work of Mortimer<sup>10</sup> suggests that this principle has to do with skeletal growth and differentiation in a manner somewhat different from its effect on muscle, for example. Mortimer showed quite clearly that the skull of the hypophysectomized young rat failed to differentiate even though some increase in size did occur. He has summarized the effects of hypophysectomy on the cranium of the rat as follows:

“A marked decrease in vascularity of bone, affecting individual bones in proportion to the abundance of their normal vascular supply, and to the degree and pattern of differentiation that they normally are called upon to undergo in growth.

“The processes of *pari passu* resorption and deposition are seriously disturbed, the former apparently being more affected than the latter.

“All growth does not cease: cranial height and width reach materially normal dimensions; antero-posterior growth suffers.

“The snout is more affected than the brain-case; growth is inadequate in all directions.

“A roentgenologic diagnosis of completeness of the operation can be rapidly and reliably arrived at from the following observations: the cranium is small for the age and sex of the animal; the snout is disproportionately small relative to the brain-case. The calvarial outline corresponds, *in form*, to about the age at which the animal was hypophysectomized, although the dimensions may have increased. The middle table in the calvaria is hypoplastic, and in consequence presents the appearance of being obliterated, especially in the parietal bone. The frontal sinus-homologue is hypoplastic. The characteristic tooth changes described by Schour and Van Dyke are seen.”

Mortimer was able to show that these defects could be corrected to a large degree by treatment with the growth hormone (Q fraction).<sup>11</sup> This fraction seemed to have a specific effect upon the vascularity of bone, restoring the normal architectural structure of the diploe, the frontal sinus homologue, and cancellous bone throughout the cranium. There resulted a satisfactory growth and differentiation in the snout, and the incisor teeth showed a normal x-ray appearance in the part grown after treatment was started.

The favorable effects of treatment of hypophysectomized animals with certain anterior lobe growth extracts upon protein metabolism<sup>12</sup> and upon calcium balance are due most likely to the action of the growth hormone.<sup>13</sup>

The growth hormone has a specific chondrotrophic action. This fact has been established by the work of Silberberg<sup>14</sup> and more recently by that of Freud, Levie and Kroon.<sup>15</sup> These latter authors, who have published a most valuable contribution to this phase of the subject, have summarized their findings as follows: “After hypophysectomy, longitudinal bone growth ceases, especially in the tail, and seven days after operation the difference between operated and control animals may be readily detected in skiagrams. The epiphyses are closed soon after hypophysectomy. Epiphyseal closure, once completed, cannot be reversed by treatment with growth hormone. Growth hormone treatment, when commenced immediately after hypophysectomy, prevents epiphyseal closure and maintains normal longitudinal growth in the tail. The assay of growth hormone is simple and reliable, using as indicator the tail length and vertebral development as shown by serial skiagrams. A minimal requirement of 6 mm. growth is advised as a basis of comparison between unknown and reference standard preparations. The growth defect after hypophysectomy is definitely localized in the growing epiphyseal cartilage. The histologic features of the process of growth cessation after hypophysectomy are exactly analogous to those exhibited at the end of the normal growth period. Hypophysectomized rats show no alteration in the development of bone tissue, and desmal bone, such as cranial bone, develops normally. Growth hormone has a biologically typical point of attack at the proliferating cartilage and the terms growth hormone and chondrotrophic hormone are therefore synonymous.”

tinued from the thyrotrophic substance. The corticotrophic substance has no other known function than that of maintaining the cortex of the adrenal in a normal functioning condition.

*Ketogenic Substance.*—Since Burn and Ling<sup>61</sup> first showed that a simple alkaline extract of anterior pituitary glands caused a greatly increased ketosis in rats on a butter diet, numerous investigations have been made on the subject. It has been my experience that almost any protein fraction obtained from anterior pituitary tissue may manifest ketogenic properties when administered to sensitive test objects such as the fasting rat or mouse. It has been found in growth extracts, in thyrotrophic extracts and in prolactin preparations. Very recently Neufeld and Collip<sup>62</sup> have shown that the substance in pituitary extracts responsible for the ketogenic effect is thermostable over a certain pH range. It can be boiled, for example, in N/10 HCl without much loss in activity, and in this manner it can be differentiated from most other anterior lobe principles. All active ketogenic extracts cause an increase in the total lipid content of the liver.

*Prolactin.*—Prolactin appears to be purely a secretagogue to the fully developed mammary gland. Riddle and Bates<sup>63</sup> have shown that potent extracts containing this hormone can be prepared which are free of growth, thyrotrophic and gonadotrophic properties. White and others<sup>64</sup> have obtained a crystalline product which has only prolactin properties so far as they have been able to ascertain.

*Diabetogenic Substance.*—The property of anterior lobe extracts of inhibiting the hypoglycemic effect of insulin was first described by Houssay and Potlick<sup>65</sup> in hypophysectomized toads. A truly diabetogenic action of certain simple extracts of anterior lobe tissue was shown by Evans and others<sup>66</sup> in the dog. Shortly thereafter, Houssay and others<sup>67</sup> obtained similar results. More recently Young<sup>68</sup> has confirmed the diabetogenic action of freshly prepared crude extracts of fresh anterior lobe tissue. Young showed that the induced diabetic state persisted in some dogs after the cessation of injections. Campbell and Best<sup>69</sup> have been able to confirm Young's work. They also made the very important observation that the pancreas of a normal animal rendered diabetic by anterior pituitary extract treatment contained little or no insulin. Some points established by Young are worthy of special note: (1) Preparation and conservation of the extract at low temperature are essential. (2) Individuals of certain species (mouse, rat, and guinea pig) are almost completely insensitive to diabetogenic extracts effective in dogs. (3) The dog is the best animal in which to demonstrate the effect.

Young<sup>70</sup> has emphasized that the true diabetogenic activity of extracts should be clearly differentiated from simple hyperglycemic responses occurring within a few hours of the injection of the extract. The extracts which he has used successfully had little or no effect upon the blood sugar level within a few hours of injection.

*The Glycotrophic Substance.*—Certain anterior lobe extracts inhibit the hypoglycemic action of insulin and as a rule such extracts also cause an increase in muscle and liver glycogen. This latter action has been described as the glycotrophic effect by Young.<sup>71</sup> In all probability this is the same as the so-called glycostatic effect of Russell and Bennett.<sup>72</sup> These workers observed that the diminution in carbohydrate stores in hypophysectomized rats could be restored by appropriate treatment with anterior lobe extract.

*The Specific Metabolic Principle.*—Although this article deals specifically with anterior lobe principles, it would not be complete without reference to the substance present in all simple extracts of pituitary tissue, whole gland or dissected anterior and posterior lobes, which has the property of elevating the metabolic rate presumably by direct action in the periphery. So much attention has been paid by investigators in the field of pituitary physiology to the trophic principles that perhaps the importance of the pituitary as a source of active principles which are not trophic in function but which act directly upon certain phases of the metabolic processes has not been sufficiently stressed.

The early work of Houssay and Artundo<sup>73</sup> who found that in thyroidectomized dogs the metabolic effect of pituitary extracts, though reduced, was still present, of Gaebler<sup>74</sup> who demonstrated an increase in metabolism in thyroidectomized dogs treated with an anterior lobe extract, and of Riddle and associates<sup>75</sup> in which

ectomized guinea pigs. This they attributed to stimulation of midbrain centers by some constituent of the extract used. Gaebler<sup>51</sup> has shown that the basal metabolism of thyroidectomized dogs can be raised by anterior lobe extracts containing thyrotrophic hormone. Recent work in my laboratory<sup>52</sup> has shown quite conclusively that the factor responsible for the increase in metabolism in the thyroidectomized animal is not the thyroid-stimulating hormone, but a specific hormone substance probably produced in the pars intermedia. In this same connection, mention should be made of the work of Riddle and others<sup>53</sup> who showed that their prolactin preparation raised the basal metabolic rate in the thyroidectomized pigeon.

*The Gonadotrophic Hormone(s), or Maturity Factor(s).*—The demonstration by Smith and Engle<sup>54</sup> and by Zondek and Aschheim<sup>55</sup> of the gonadotrophic effects of implantations of anterior lobe tissue formed the basis for all the work of recent years which has established that the anterior lobe, by virtue of its hormone influence and control of the gonads, is of paramount importance in all phases of sex physiology. There are two main types of physiologic effect of gonadotrophic preparations of anterior lobe tissue upon the ovary: (1) maturation of immature follicles and (2) luteinization. Evidence obtained from work with extracts points to the mediation of these two effects by two separate and distinct substances. There is also indirect evidence that the intact pituitary may under certain circumstances produce more or less of either of these two substances. The problem is complicated further by the fact that extracts of human placenta, pregnancy blood, and urine contain a gonadotrophic substance which is not identical with the anterior lobe gonadotrophic substance. Also, pregnant mare's serum contains a gonadotrophic substance which is comparable in its physiologic effects with true anterior lobe gonadotrophic hormone and not with human placental gonadotrophic hormone. Space will not allow of a discussion of the interesting and fascinating experimental work which has been done with each of these three gonadotrophic substances. The reader is referred, accordingly, to the very excellent monographs of H. B. Van Dyke.<sup>1, 2</sup>

A point of great practical interest is the close association in extracts of the anterior lobe of the thyrotrophic and gonadotrophic substances. There is a considerable variation among different species of the thyrotrophic and gonadotrophic potency of the anterior lobe. This fact can be turned to practical use in the preparation of extracts. Thus the anterior lobes of cattle have a relatively low content of gonadotrophic substance and a relatively high content of thyrotrophic hormone; the anterior lobes of sheep present the reverse condition, while those of pigs have a high content of each of these factors.

There is now experimental evidence to show that the discharge of gonadotrophic hormone from the intact pituitary of the postpubertal human female is rhythmic. This hormone may be detected in the urine, and quantitative methods are available for its estimation. Recently Venning, Henry, and Browne<sup>56</sup> have introduced a quantitative method for the estimation of pregnandiol in the urine. Since pregnandiol appears to be an index of luteal hormone metabolism, this allows of an indirect but probably fairly accurate determination of the duration and amount of luteal activity. It is therefore possible to estimate the functional activity of the anterior lobe as regards its ovary-stimulating action and to determine fairly accurately, as Venning and Browne have done, the time of ovulation and the duration of the luteal phase in individual cases. It would be difficult to overestimate the importance of the development of quantitative methods such as these and others to the clinical study of problem cases of disturbed pituitary or ovarian function, of abortion and of the toxemias of pregnancy.

*The Corticotrophic Hormone.*—Smith<sup>57</sup> showed that marked atrophy of the adrenal cortex took place following hypophysectomy in rats and that this degenerative change could be prevented or the normal condition restored by intramuscular implantations of fresh rat pituitaries. Collip, Anderson and Thomson<sup>58</sup> showed that the restoration of the atrophic cortex of the hypophysectomized animal was not due to the thyrotrophic hormone, as some had supposed, but to another specific substance which could be separated from the thyrotrophic hormone by virtue of its greater solubility in aqueous alcohol and the fact that it could be precipitated isoelectrically. Anselmino and others<sup>59</sup> and Friedgood<sup>60</sup> also showed that the corticotrophic is dis-

6. All of the active principles which have been mentioned are insoluble in absolute alcohol.

7. The growth principle, one fraction of the thyrotrophic substance, prolactin and the corticotrophic hormones are all precipitable isoelectrically.

8. Gonadotrophic hormone cannot be precipitated isoelectrically. This is true also for one fraction of the thyrotrophic substance.

9. The growth principle can be adsorbed upon  $\text{Ca}_3(\text{PO}_4)_2$  from neutral or slightly alkaline solutions and can be released by washing with ice-cold dilute aqueous alkali.

10. Practically all of the anterior lobe principles are more or less heat-stable over a definite pH range.

The methods of preparing and fractionating anterior lobe extracts are innumerable, and each worker in this field has his own preferences and dislikes in the matter of procedure. Often the same end result can be accomplished by entirely different methods of approach. Recently I have outlined the methods of extraction which I prefer to use in my own work.<sup>97</sup> I would make no claim, however, that these are better than those used successfully by others.

### ANTIHORMONES

No discussion on anterior pituitary hormones would be complete without some reference to the subject of antihormones.

The fact has been known for many years that long-continued treatment of experimental animals with certain hormone preparations may lead to the development of a state of resistance to the physiologic effects of such extracts. This resistant state has been demonstrated, in the case of anterior lobe extracts, to the thyrotrophic,<sup>98</sup> the gonadotrophic,<sup>99</sup> the ketogenic,<sup>100</sup> and the growth effects<sup>9a</sup> of certain extracts. Collip and Anderson<sup>101</sup> showed that the blood serum of thyrotrophic hormone resistant animals contains a substance which is antagonistic to the thyrotrophic hormone and that previously untreated animals injected with blood serum containing this substance can be made resistant for a time to injections of extracts containing the thyrotrophic hormone. The existence of antigonadotrophic substances,<sup>99c, d, e, 102</sup> an antiketogenic<sup>103</sup> and an antilactogenic<sup>104</sup> substance in the blood serum of animals chronically treated with appropriate extracts has been established.

As a possible explanation of such experimental results, Collip proposed the antihormone theory.<sup>9a, 105</sup> This theory gives expression to the view that the antagonistic or inhibitory substance is a normal constituent of the blood and tissues; that there is a balance between a positively acting hormone substance and a hypothetical antagonist, the antihormone; and that it is only when this balance is greatly disturbed and the relative as well as absolute amount of antihormone is greatly increased that the latter can be detected. Many are of the opinion that all "antihormone" reactions are basically immunologic in type.<sup>106, 107</sup> Undoubtedly, immunological reactions do play an important part in many of the antihormone reactions that have been described, since the extracts used contain protein which, even in the case of those made from the glands of the same species of animal as is used in testing,<sup>108</sup> may be considered as "foreign." Since antihormones have been shown to occur spontaneously in the blood serum of certain patients, and since there is evidence that the native secretion of the anterior lobe may be inhibited by the injection of antihormone serum,<sup>105b, 109</sup> the exact significance of the antihormone reaction must remain to be disclosed by future work. The fact that pre-treatment with certain hormones will cause the appearance in the blood of principles antagonistic to these hormones may be regarded as established beyond doubt.\*

### SUMMARY OF RECENT WORK

Before bringing this discussion to a close, I should like to report on the developments to date of work in my laboratory along somewhat new lines with certain pituitary extracts. It is impossible to state at this time the exact significance of certain observations which I shall describe.

an increased basal metabolic rate was obtained in thyroidectomized pigeons treated with a preparation of prolactin, showed that the metabolic rate could be elevated by anterior lobe extracts otherwise than by stimulation of the thyroid by the thyrotrophic substance. Extensive investigations have been made upon this metabolic stimulant within the past three years by my collaborators Drs. O'Donovan, Billingsley, Neufeld and Denstedt.<sup>52, 62, 75-92</sup> The chief points of interest which have been established as a result of these investigations are: (1) The active principle is remarkably thermostable in aqueous solution. It has been boiled in 2 per cent  $\text{NH}_4\text{OH}$  for one hour with little loss in potency. It can be boiled in  $\text{N}/10$   $\text{NaOH}$  for a few minutes with comparative safety, but long heating in this alkaline medium has caused destruction of the active principle. Some activity has been observed by Dr. Denstedt in a preparation after boiling for ten hours in  $\text{N}/4$   $\text{H}_2\text{SO}_4$ . The active principle has been successfully dialyzed and in electrodialysis experiments it has been found to migrate to the kathode cell. It is resistant to peptic digestion, but has been destroyed by prolonged treatment with trypsin.

(2) Injection of a potent preparation of this hormone into rabbits, guinea pigs, rats, or human subjects<sup>93</sup> has caused the metabolic rate to be sharply elevated for a period of a few hours following each injection. Our most extensive studies of this hormone have been made on normal, thyroidectomized and hypophysectomized rabbits. Associated with the increase in oxygen consumption in either fed or fasted animals, there is a depression in the respiratory quotient which is more marked in the former. This, together with other findings in connection with carbohydrate and nitrogen metabolism, suggests that the hormone specifically stimulates the metabolism of fat.

(3) Because of its close association with the melanophore-expanding hormone of the pars intermedia, it is probably of pars intermedia origin. Recent work has shown that it is not identical with the melanophore hormone.<sup>90, 94</sup> It has been differentiated from the ketogenic substance,<sup>62a</sup> and also from the substance which antagonizes the hyperglycemic action of adrenalin.<sup>62b</sup> This latter substance appears from our recent studies to be a posterior lobe principle separate and distinct from the well known oxytocin and vasopressin.

#### THE PREPARATION OF EXTRACTS

The alkaline extract of fresh anterior lobes first described by Evans,<sup>95</sup> and later modified slightly by others,<sup>96</sup> is an excellent starting point for the fractionation of the specific principles. Indeed, for much physiologic experimental work the simple alkaline extract, adjusted to a pH of about 7, at which point much protein material can be removed by centrifugation, is very satisfactory. Such an extract, though necessarily relatively dilute, contains some of practically all of the known active principles. All of these, so far as can be judged in the limited state of our knowledge at present, appear to be of protein nature or else so closely linked with protein as to be inseparable from protein substances. The preparation of physiologically pure or nearly physiologically pure hormone fractions has been accomplished by obtaining in various fractions, proteinlike material possessing slightly different physical properties. The methods by which anterior lobe material can be treated to prepare active extracts are innumerable. There are, however, a number of basic principles which should be adhered to in the preparation of any extract. These principles are:

1. The necessity of using fresh material. If this is not available, fresh glands that have been frozen and kept frozen until they are ready for use, or fresh glands that have been preserved in alcohol or acetone are moderately satisfactory. Dry powders prepared from defatted fresh glands, in vacuo and at low temperatures, are also quite good.

2. All of the known active principles are soluble in dilute aqueous alkali.

3. All of the active principles can be precipitated from aqueous solution on saturation with  $(\text{NH}_4)_2(\text{SO}_4)$ .

4. The growth principle, the gonadotrophic and thyrotrophic substances, are practically insoluble in high concentrations of neutral ethyl alcohol.

5. The corticotrophic principle, the thyrotrophic and gonadotrophic principles and prolactin are freely soluble in alkaline alcohol (70 per cent by volume).

may be misleading and that clinical results may be obtained (as presumably they were in the cases mentioned) with specially prepared extracts which may be without visible effect on the ovaries of the normal rat. A clinical trial of standardized extracts of corticotrophic and specific metabolic principles is now being undertaken and the results of these experiments may throw some further light on the etiology of certain types of menstrual disorders.

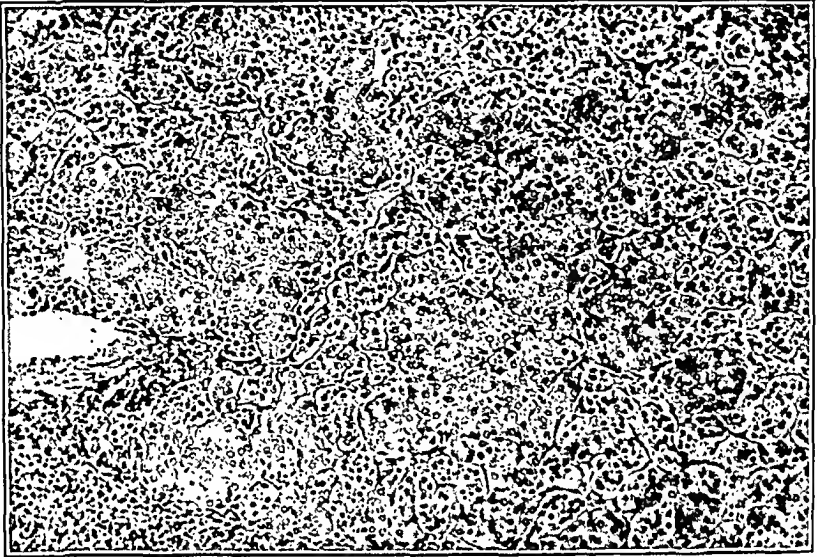


Fig. 1.—High power of adrenal medulla of an hypophysectomized rat treated for sixteen days with the medullotrophic extract by feeding. Note the hypertrophy of the "dark cells".

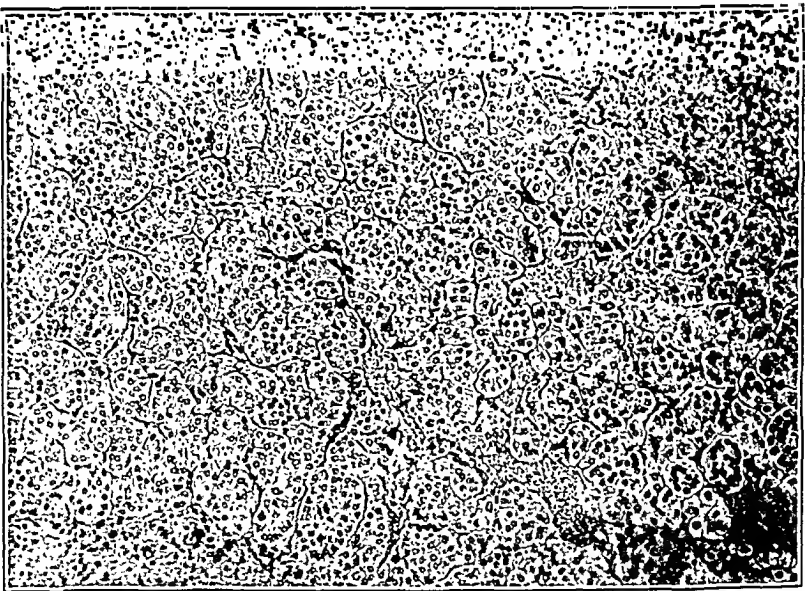


Fig. 2.—High power of adrenal medulla of an hypophysectomized rat treated for nine days with a corticotrophic preparation by subcutaneous injection. Both cortex and medulla are comparable to similar tissues in normal animals.



1. Preliminary experiments to determine the effect of daily injections into chickens of a pituitary extract rich in the specific metabolic factor, carried out at Macdonald College with the cooperation of the Departments of Poultry and of Chemistry and under the supervision of Professors Maw and MacFarlane, have shown that such treatment may cause decolorization of the depot fat. This suggested that the metabolism of vitamin A might be influenced by the treatment. Already sufficient data have been obtained to show that significant changes in the vitamin A content of liver and blood may be produced by treatment of chickens in this manner. These results suggest that there may be a definite relationship between certain phases of pituitary activity and the metabolism of vitamin A.

2. A clinical trial of the same type of extract in a small group of obese women was undertaken by Dr. I. M. Rabinowitch. This was done since it had been shown that the specific metabolic hormone had similar effects on the metabolic rate and the respiratory quotient in man<sup>93</sup> as it had in rabbits.<sup>52</sup> Some rather unexpected results were obtained. As a therapeutic aid to weight reduction in the cases studied no encouraging result was obtained. It so happened that most of the subjects treated had some degree of menstrual irregularity, and in four of eight cases treated the patients stated, without any leading question, that it was the first time in years that they had noted any regularity at all. Since the particular extract used had received heat treatment on a boiling water bath twice during its preparation at pH 5 and 10 and again during sterilization, there was little likelihood of any gonadotrophic or thyrotrophic principles surviving such treatment, and by actual test negative results have been obtained for these. The extract did contain a small amount of the substance which neutralizes the action of a standard gonadotrophic preparation when tested in the approved manner, namely by subcutaneous injection of the gonadotrophic substance and intraperitoneal injection of the antagonist. It has been proved also on test to have a high titre of corticotrophic substance. If it be assumed that the re-establishment of menstrual rhythm in the cases above mentioned was due to the treatment and that it was not fortuitous, the beneficial result might be attributed to a general improvement in metabolism due to the metabolic principle. It might equally well be attributed to the inactivated (by rat test) gonadotrophic substance in the extract or indeed to the antagonist. Since the latter is only active in the rat when administered intraperitoneally and since the patients were injected subcutaneously, it is difficult to understand how this might have been a factor.

I do not wish to appear to put undue emphasis on these observations, but in view of the fact that, on the whole, clinical experience with gonadotrophic preparations has been somewhat disappointing, it appears to me that many new avenues of treatment with new types of pituitary extracts should be explored. It is possible that the present method of standardizing gonadotrophic extracts in terms of rat units

\*For an extensive review of the literature on this subject see Collip, Selye and Thomson, *Biological Reviews* (in press).



rats treated with a corticotrophic preparation by injection, complete restoration of the cortex with no visible change in the medulla and in other hypophysectomized animals treated with the medullotrophic preparation by mouth no appreciable change in the atrophic cortex but a strong positive reaction in the nature of hypertrophy of the

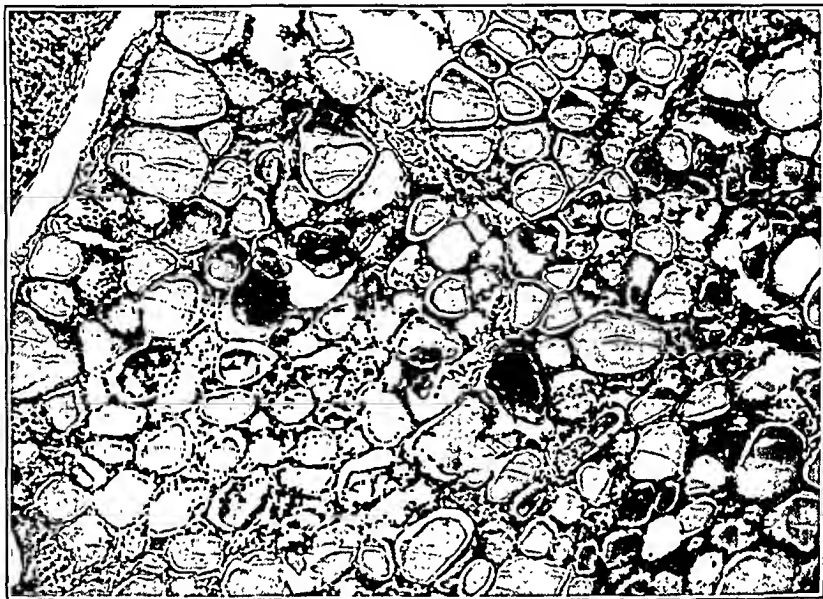


Fig. 5.—Atrophic thyroid of hypophysectomized rat treated with medullotrophic hormone; from same animal as shown in Fig. 1.

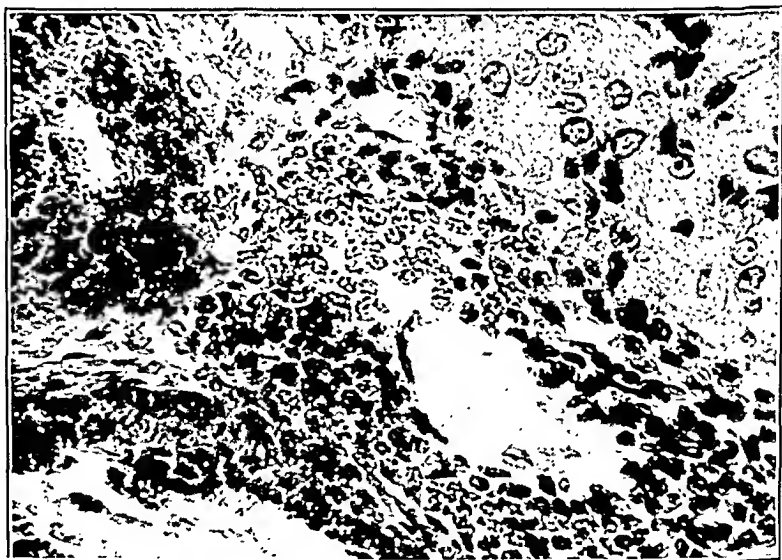


Fig. 6.—Atrophic ovary with wheel cells of hypophysectomized rat treated with medullotrophic hormone; from same animal as Fig. 1.

dark cells of the medulla (see Figs. 1 to 6). Clinicians, I am sure, will be interested to know that it was upon clinical evidence obtained following the oral administration of a certain extract that I was testing that I became convinced that an active principle was concerned. Sub-

3. Probably the most important of the investigations relating to the physiology of the pituitary in which I have been interested has been my recent finding of a medullotrophic principle in primary alcoholic extracts of prime gland tissue.<sup>110</sup> This principle has also the remarkable quality of being orally active. It would appear from the investigations which I have so far been able to make with it, to be trophic to the so-called "dark cells" of the adrenal medulla. The diagnostic test for the active substance consists in the production of hypertrophy

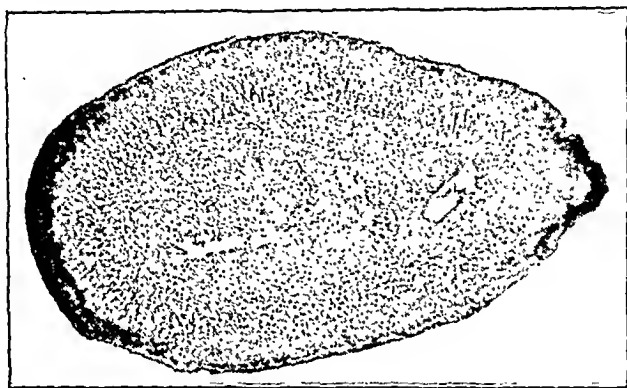


Fig. 3.—Cross section of adrenal of hypophysectomized rat showing atrophy of cortex and hypertrophy of dark cells of medulla. This is a low power photomicrograph of same section as shown in high power in Fig. 1.

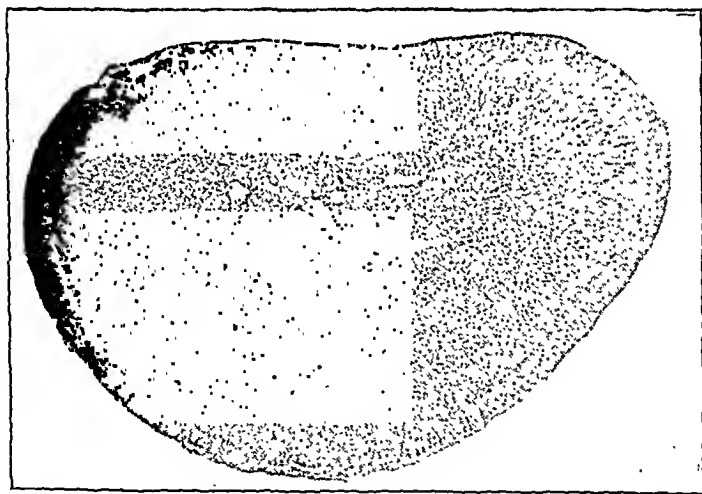


Fig. 4.—Cross section of adrenal gland of hypophysectomized rat treated with corticotrophic hormone. This is same section as shown in high power in Fig. 2.

of these special cells in the medulla of hypophysectomized rats. This test can also be used to assay the potency of different preparations. It is in many respects similar to the test used in this laboratory for corticotrophic hormone. In this latter test the restoration of the atrophic cortex of the hypophysectomized rat toward or to normal forms the basis for assay of corticotrophic extracts. In my earliest experiments on the differentiation of the corticotrophic from the medullotrophic hormone I was able to demonstrate in hypophysectomized

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stantiation of this conviction was realized when the medullotrophic action of the extract was established in hypophysectomized rats treated by the oral route. All of the evidence so far available would seem to show that this orally active pituitary principle does not act upon the chromaffin system. The intensive and fruitful work which has been going on for some years now in many laboratories upon problems of adrenal physiology and chemistry serves to show how very complex are the functions of the adrenal gland. The close association between the adrenal cortex and the gonads has long been recognized, as has also the relationship of the medulla to the sympathetic nervous system. It would appear from the experimental studies described in brief above that the medulla may have still another function subserved through its so-called dark cells. Since potent preparations of the corticotrophic hormone satisfactory for administration by injection to the human subject can now be made, and since the medullotrophic substance can be administered safely by the oral route, the clinician will have two agents, each of which can be biologically standardized, with which to influence at least two functions of the adrenal glands.

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effort has been made on the part of one observer to carry the problem through in the same patient from onset of pregnancy, through labor and the puerperium. Truly, excellent observations have been made for individual members of the group of lipids through pregnancy. Detailed studies are available for individual patients at term, in labor, and during the puerperium. Boyd<sup>3</sup> presents a most complete picture of the lipemia of pregnancy at term. We have not found published any complete lipid studies on the same individual from the early weeks of pregnancy through gestation.

Numerous observers have demonstrated the so-called lipemia of pregnancy and Bloor and later Boyd have discussed the similarity of this lipemia to changes in blood lipids associated with various constitutional disease conditions. It is not within the province of this present discussion to go into the origin of the lipemia of pregnancy. Rather, we should like to present our findings as a preliminary study of blood lipids during normal pregnancy. From various clues we have obtained in this study we expect to carry this work further, possibly adding something to the question of how the fetus gets its lipids.

Most of the literature concerning lipids in pregnancy has to do with cholesterol studies. Hermann and Neumann<sup>4</sup> reported an increase of blood cholesterol esters during pregnancy. Slemons and Curtis<sup>5</sup> reported an absence of cholesterol esters in fetal blood when no anesthesia was employed and concluded that the placenta was impermeable to this fraction of blood lipid. Slemons and Stander<sup>6</sup> showed that the large quantity of fat in maternal blood was not associated with a corresponding change in the circulation of the fetus and further concluded that the placenta was impermeable to fat and lipid. Gardner and Gainsborough<sup>7</sup> reported that free cholesterol increases during pregnancy to the thirtieth week with a decrease in ester cholesterol to about the same time. In their series, there occurs then, a reversal of curve so that at parturition approximately a normal relationship exists again. Kaufmann and Mühlbock<sup>8</sup> do not note this fluctuation but report little variation from the second month of gestation to term. Plass and Tompkins<sup>9</sup> reported total and lipid phosphorus much higher in maternal than fetal blood serum; they also note that sex and birthweight have no influence on blood phosphorus. These observers feel that fats and lipids are probably synthesized in the fetal organism. Mühlbock<sup>10</sup> concludes that from the fourth month to term there is a progressive increase in iodine-combining power which is similar to the hyperlipemia of pregnancy, indicating an increase in unsaturation of the fatty acids during pregnancy.

Boyd<sup>3</sup> has shown that the red blood cells show no marked variation in lipid composition during pregnancy. The significant changes in lipid concentrations of the blood are noted in the blood plasma or serum. Boyd demonstrated that the total lipids of blood plasma during pregnancy are increased on the average to one-half as high again as in the nonpregnant. All of the component lipids are increased, the greatest increase being in neutral fat. Phospholipid, free and ester cholesterol are each higher than their pregestational value. The normal ratios between phospholipid, ester and free cholesterol are but slightly altered. Phospholipid and free cholesterol are each increased about 25 per cent; ester cholesterol only about 9 per cent higher. The iodine numbers of total and phospholipid fatty acids are similar in pregnancy to those of the nongravid female.

Comparisons of mean values may or may not warrant valid deductions. With the use of standard deviation formulas, sound conclusions may be drawn. Our information is presented in two forms. The graphs demonstrate the trend of concentration of the various lipid constituents through gestation and in the puerperium. It will be noted that

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### BLOOD LIPIDS IN PREGNANCY\*

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FAT metabolism in the adult, male or female, has presented some interesting problems. Leathes and Raper<sup>1</sup> in their monograph, "The Fats," discuss the synthesis of fat in animals. It is very difficult to demonstrate the formation of fat from protein. Direct evidence of a transformation of carbohydrate into fat has not been obtained in any organ. Also, the carbohydrates differ so greatly from the fats in chemical characteristics and composition that it is unlikely that the processes of transformation of carbohydrate into fat would be demonstrated easily experimentally. Furthermore, with the understanding of the processes of digestion, absorption, and intermediate metabolism, the problems of lipid synthesis from protein and carbohydrate lose much of their practical interest.

The developing product of conception presents a distinct lipid problem. The growing fetus has a definite lipid requirement for essential cell growth. This question of fat synthesis in the fetus or fat transportation across the placental barrier is a problem of magnitude comparable to that which confronted observers who solved the problems involved in fat metabolism in the adult.

It is interesting to review the facts that the fetus begins to store fat at about the same stage of gestation that the Langhans layer of cells begins to disappear from the placenta, and at about the same time that the blood lipids are beginning to show a general increase in concentration in the maternal circulation.

With the advent of a microtechnique<sup>2</sup> for determination of blood lipids, a steadily increasing literature has developed.

Until recently the studies in this phase of biologic chemistry which have been concerned with pregnancy have not been sustained. No

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ability to assign comparable results in the human being. The principle followed in this work was to do a complete lipid chemistry at monthly intervals on a series of eight pregnant women. These studies in most instances were carried out as planned; in two or three cases fewer observations are available than anticipated.

This study is as yet incomplete. All but one patient has delivered but post-partum examinations are as yet not available on all subjects.

TABLE III. BLOOD SERUM LIPIDS IN PREGNANCY

NUMBER 22373	DURATION OF PREGNANCY					DELIVERY	POST PARTUM	PER-CENTAGE INCREASE
	14 WK.	19 WK.	23 WK.	30 WK.	35 WK.			
Total lipid	766	810	844	878	992	1051		37
Neutral fat	152	267	220	218	317	368		142
Total fatty acids	436	488	503	523	622	679		53
Total cholesterol	234	252	240	245	252	248		8
Ester cholesterol	173	180	169	177	180	176		4
Free cholesterol	61	72	70	68	73	72		20
Phospholipid	264		272	297	302	318		20
Phospholipid fatty Acid I <sub>2</sub> No.	104		121	80	92	121		
Total fatty acid I <sub>2</sub> No.	117	100	107	102	99	92		
Total fatty acid } Phospholipid }	1.65		1.85	1.76	2.08	2.13		
Phospholipid }	1.12		1.13	1.21	1.19	1.28		
Total cholesterol }	0.74	0.71	0.70	0.72	0.71	0.71		
Ester cholesterol }								
Total cholesterol }								

Negro, 18 years, gravida i, estimated date of confinement Aug. 22, 1939, delivered Aug. 16, 1939, weight gain 18 pounds from fourteenth week. R.B.C. 3,600,000, Hb. 60 per cent. Urine negative. Labor 22¼ hours. Seminarcosis: Seconal—Hyoscine. Baby: 3,890 gm., breast fed. Anesthesia: 15 c.c. of CHCl<sub>3</sub>, 88 c.c. of ether.

TABLE IV. BLOOD SERUM LIPIDS IN PREGNANCY

NUMBER 35368	DURATION OF PREGNANCY					PRE-MATURE DELIVERY	POST PARTUM	PER-CENTAGE INCREASE
	12 WK.	18 WK.	21 WK.	26 WK.	30 WK.			
Total lipid	540	659	761	788	873	1103	666	104
Neutral fat	122	205	245	219	233	335	121	174
Total fatty acids	316	385	459	476	525	687	371	117
Total cholesterol	154	220	230	216	245	282	211	83
Ester cholesterol	106	156	159	147	182	201	151	90
Free cholesterol	48	64	71	70	63	81	60	70
Phospholipid	194		180	255	275	353	234	81
Pl. F. A. I <sub>2</sub> No.	79		66	62	114	94		
T. F. A. I <sub>2</sub> No.	105	106	100	104	109	95		
Total fatty acid } Phospholipid }	1.62		2.55	1.86	1.90	1.94	1.58	
Phospholipid }	1.26		0.78	1.18	1.12	1.25	1.10	
Total cholesterol }	0.68	0.70	0.69	0.68	0.74	0.71	0.71	
Ester cholesterol }								
Total cholesterol }								

Patient, white, 22 years, gravida i, estimated date of confinement Aug. 21, 1939, delivered July 10, 1939. Premature twins. Labor 10 hours and 55 minutes. Weight gain 20 pounds from twelfth week. Urine negative. R.B.C. 3,780,000, Hb. 80 per cent. Seminarcosis: Seconal, Morphia, Hyoscine. Babies: 1,650 gm., 1,820 gm., no breast. Anesthesia: 6 c.c. of CHCl<sub>3</sub>, 80 c.c. of ether.

the normal variations in concentration of lipids are great. With such a range of normal, the curve of progressive change throughout a whole pregnancy is of more importance than relationship of the patient's particular findings to an average.

The group of tables presents the detailed findings of each patient throughout her particular pregnancy. Significant points of history are added. It is from these tables that subsequent items of importance may be found.

The human subject is selected for this study because of the variable response of experimental animals, and the constant doubt as to the

TABLE I. BLOOD SERUM LIPIDS IN PREGNANCY

NUMBER 35617	DURATION OF PREGNANCY					DE-LIVERY	POST PARTUM	PER-CENTAGE INCREASE
	12 WK.	18 WK.	24 WK.	29 WK.	35 WK.			
Total lipid	481	639	765	780	851	779	639	77
Neutral fat	123	210	226	170	252	176	142	105
Total fatty acid	290	385	453	447	525	462	367	81
Total cholesterol	127	194	239	238	222	210	193	88
Ester cholesterol	93	135	171	173	154	147	135	86
Free cholesterol	34	60	68	65	68	63	58	100
Phospholipid	169	145	186	256	275	296	215	75
Pl. F. A. I <sub>2</sub> No.	102		117	108	110	113		
T. F. A. I <sub>2</sub> No.	103	112	105	99	101	107		
Total fatty acid to Phospholipid	1.71	2.65	2.43	1.35	1.90	1.56	1.71	
Phospholipid to Total cholesterol	1.33	0.74	0.77	1.08	1.23	1.40	1.11	
Ester cholesterol to Total cholesterol	0.73	0.69	0.71	0.72	0.69	0.70	0.70	

Negro, 19 yr., gravida i, estimated date of confinement Aug. 17, 1939, delivered Aug. 3, 1939, weight gain 27 pounds from eleventh week. R.B.C. 3,370,000, Hb. 75 per cent. Urine negative. Labor 11¼ hours. Semimarcosis: Dilaudid-Hyoscine. Baby: 2,480 gm., breast fed. Anesthesia: 15 c.c. of CHCl<sub>3</sub>, 50 c.c. of ether.

TABLE II. BLOOD SERUM LIPIDS IN PREGNANCY

NUMBER 21747	DURATION OF PREGNANCY			DELIVERY	POST PARTUM	PER-CENTAGE INCREASE
	20 WK.	33 WK.	40 WK.			
Total lipid	672		1006	911	791	50
Neutral fat	155		309	249	210	100
Total fatty acids	390	577	623	551	472	60
Total cholesterol	200	210	268	247	224	35
Ester cholesterol	140	142	197	172	156	40
Free cholesterol	60	68	71	75	68	25
Phospholipid	224	189	297	300	253	34
Pl. F. A. I <sub>2</sub> No.		96	99	100		
T. F. A. I <sub>2</sub> No.	107	90	93	101		
Total fatty acid to Phospholipid	1.74	3.00	2.09	1.83	1.87	
Phospholipid to Total cholesterol	1.12	0.90	1.10	1.21	1.13	
Ester cholesterol to Total cholesterol	0.70	0.67	0.73	0.69	0.69	

Patient, white, 27 years, gravida ii, estimated date of confinement June 5, 1939, delivered June 10, 1939, weight gain 22 pounds from twentieth week. R.B.C. 4,370,000, Hb. 80 per cent. Urine negative. Labor 5½ hours. Semimarcosis: Seconal-Hyoscine. Baby: 3,720 gm., breast fed. Anesthesia: 4 c.c. of CHCl<sub>3</sub> for delivery.



TABLE VII. BLOOD SERUM LIPIDS IN PREGNANCY

NUMBER 35633	DURATION OF PREGNANCY								DELIVERY	POST PARTUM	PERCENTAGE INCREASE
	11 WK.	15 WK.	19 WK.	23 WK.	27 WK.	32 WK.	37 WK.	40 WK.			
Total lipid	554	638	879	875	1049	1038	1221	1205	1167	943	122
Neutral fat	169	170	187		219	270	267	297	246	246	76
Total fatty acid	337	380	501		601	602	710	709	662	554	108
Total cholesterol	156	185	275	293	314	332	363	355	368	286	136
Ester cholesterol	110	136	204	210	222	242	274	264	268	209	150
Free cholesterol	46	49	71	83	92	90	88	91	100	77	113
Phospholipid	158	192	280	367	368		408	377	374	272	160
Pl. F. A. I <sub>2</sub> No.	61	63	91		94		92		101		
T. F. A. I <sub>2</sub> No.	98	102	93	121	107	99	101		104		
Total fatty acid	2.13	1.98	2.14		1.63		1.74	1.88	1.77	2.04	
Phospholipid											
Phospholipid	1.01	1.03	1.01	1.25	1.14		1.12	1.06	1.01	0.95	
Total cholesterol											
Ester cholesterol	0.70	0.73	0.74	0.71	0.70	0.72	0.75	0.74	0.73	0.73	
Total cholesterol											

Patient, white, 18 years, gravida ii, estimated date of confinement Aug. 1, 1939, delivered Aug. 5, 1939, weight gain 29 pounds from eleventh week. R.B.C. 4,750,000, Hb. 85 per cent. Urine: Trace of sugar last month. Seminarcosis: Seconal—Morphia—Hyoscine. Baby: 3,170 gm., breast fed. Labor 13½ hours. Anesthesia: CHCl<sub>3</sub> 6 c.c., ether 45 c.c.

post-prandial lipemia is not produced until the amount of ingested fat reaches 200 gm.

The method used in these analyses is that described by Boyd<sup>13</sup> with several minor changes of our own. This technique is the most recently published modification of Bloor's<sup>2, 14</sup> micromethod of lipid determinations. Iodine numbers were calculated as suggested by Yasuda<sup>15</sup> and complemented by Boyd.<sup>16</sup>

## RESULTS

Graphs 1 to 4, inclusive, demonstrate the variations of the individual members of the blood serum lipids throughout pregnancy from the first sample through the puerperium. On these graphs are charted the findings of each patient for each constituent lipid.

All serum lipids show a steady increase in value from the first observation to term. The increment of all these serum lipids is essentially a gradual one. Even with neutral fat, which is stored late in gestation, there is no abrupt rise in the latter months of pregnancy.

Tables I to VII, inclusive, give a composite picture for each patient. Here again we note a great variation in values for the same serum lipid among the various subjects.

The percentage increase for total lipids varied from 34 to 122 per cent; of neutral fat, from 44 to 172 per cent; of total fatty acids, from 30 to 117 per cent; of total cholesterol, from 8 to 136 per cent; of ester cholesterol, from 4 to 150 per cent; of free cholesterol, from 20 to 113 per cent; of phospholipid, from 20 to 160 per cent.

Neutral fat values showed the greatest percentage increase at term, compared to the first calculations in early pregnancy in six of seven sets of calculations.

These findings are essentially in accord with variations in the various lipid values in normal, nonpregnant individuals.

The women in this series were selected without special regard for age, color, parity, or habitus. They were all patients in the out-patient department. Their habitual diet was not supervised beyond the usual dietary instructions given all prenatal cases. Blood was drawn between 2:00 and 3:00 P.M., during usual clinic hours. The patients were not requested to refrain from food. Man and Gildea<sup>11</sup> have not found any relation between variations in serum lipids and changes in body weight, food intake, hemoconcentration, the menstrual period or season of the year. Boyd<sup>12</sup> notes that in normal man a consistent and significant

TABLE V. BLOOD SERUM LIPIDS IN PREGNANCY

NUMBER 31075	DURATION OF PREGNANCY					DELIVERY	POST PARTUM	PER-CENTAGE INCREASE
	18 WK.	23 WK.	28 WK.	38 WK.	42 WK.			
Total lipid	860	904	1123	1170	1222	1305	1148	52
Neutral fat	190	265	259	298	451	384	329	137
Total fatty acids	510	543	654	692	793	805	702	58
Total cholesterol	233	270	332	342	291	342	311	42
Ester cholesterol	172	202	240	253	206	243	226	47
Free cholesterol	61	68	92	89	85	99	85	62
Phospholipid	322		372	361	343	417	357	30
Pl. F. A. I <sub>2</sub> No.			111	107		100		
T. F. A. I <sub>2</sub> No.		110	107	99		88		
Total fatty acid	1.58		1.75	1.91			1.97	
Phospholipid								
Phospholipid	1.38		1.12	1.05			1.15	
Total cholesterol								
Ester cholesterol	0.72	0.74	0.72	0.74			0.73	
Total cholesterol								

Patient, white, 20 years, gravida ii, estimated date of confinement July 17, 1939, delivered Aug. 9, 1939, weight gain 26 pounds from eighteenth week. R.B.C. 4,520,000, Hb. 80 per cent. Urine negative. Labor 4 hours and 35 minutes. Semimarcosis: Seconal—Hyoscine. No anesthesia. Baby: 3,540 gm., breast fed.

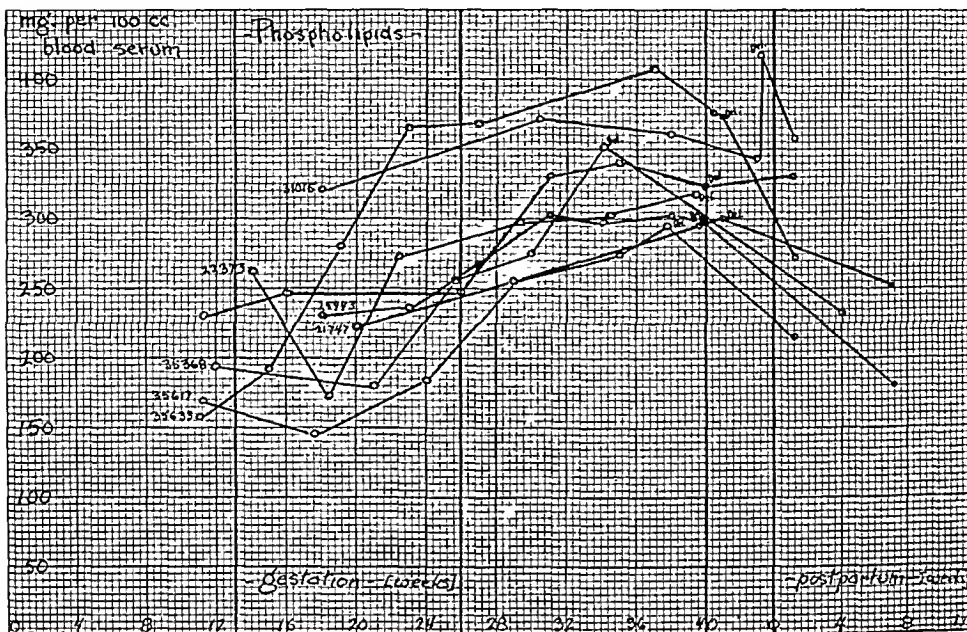
TABLE VI. BLOOD SERUM LIPIDS IN PREGNANCY

NUMBER 25943	DURATION OF PREGNANCY						DE-LIVERY	POST PARTUM	IN-CREASE, %
	18 WK.	23 WK.	27 WK.	31 WK.	34 WK.	38 WK.			
Total lipid	699	821	894	940	920	940	908	513	34
Neutral fat	206	262	297	241	222	246	272	84	44
Total fatty acid	435	513	565	561	540	567	566	281	30
Total cholesterol	177	276	225	266	270	260	229	168	56
Ester cholesterol	126	161	156	194	198	197	166	124	57
Free cholesterol	51	55	69	72	72	63	63	45	41
Phospholipid	232	235	267	303	296	302	296	180	31
Pl. F. A. I <sub>2</sub> No.	89	84	90	93	96	96	107		
T. F. A. I <sub>2</sub> No.	106	98	99	102	99	97	95		
Total fatty acid	1.87	2.18	2.11	1.85	1.82	1.87	1.91		
Phospholipid									
Phospholipid	1.31	1.09	1.18	1.14	1.49	1.16	1.29		
Total cholesterol	0.71	0.74	0.69	0.72	0.73	0.75	0.72		
Ester cholesterol									
Total cholesterol									

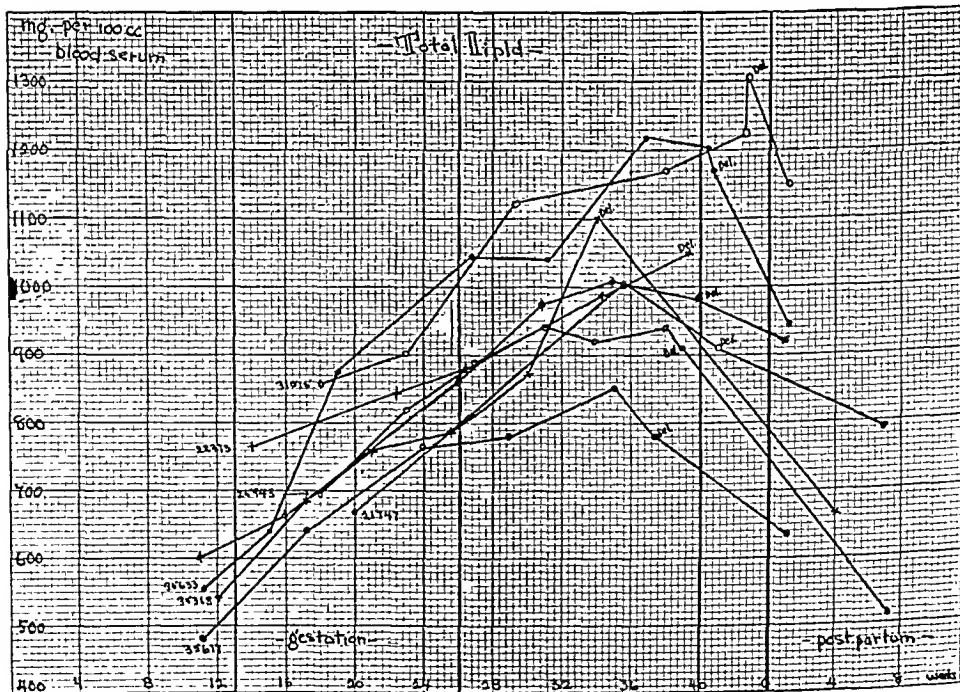
Patient, white, 24 years, gravida ii, estimated date of confinement June 17, 1939, delivered June 17, 1939, weight gain 24 pounds from eighteenth week. Urine negative. Labor 5 $\frac{3}{4}$  hours. Semimarcosis: None. Baby: 4,080 gm., breast fed. Anesthesia: 7 c.c. of CHCl<sub>3</sub> for delivery.

Free and ester cholesterol are noted to be increased in value in the blood serum during pregnancy. In 5 of 7 patients the ester cholesterol was uniformly higher in percentage increase throughout gestation; in two cases the free cholesterol was higher.

The ratio of ester cholesterol : total cholesterol remained remarkably constant throughout pregnancy in all patients.

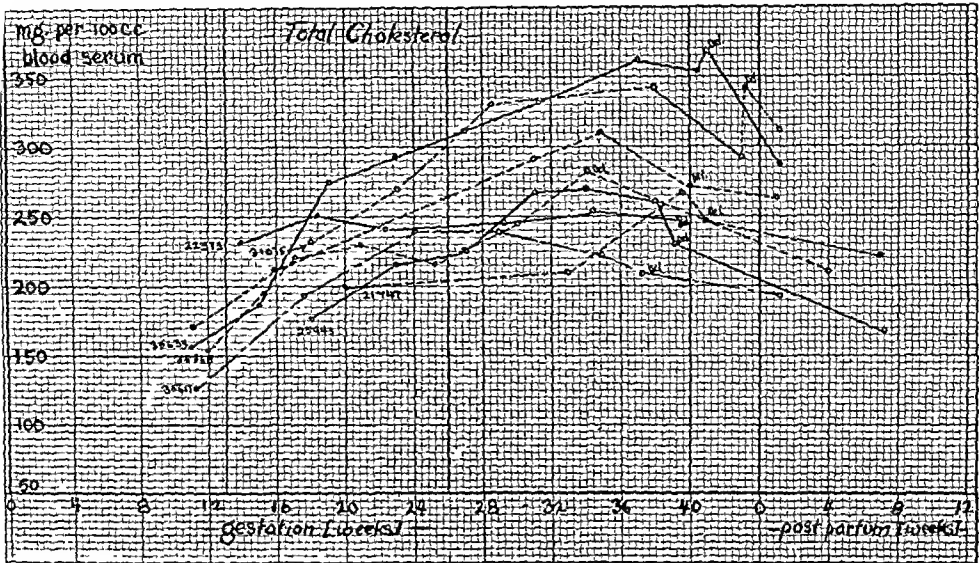


Graph 3.

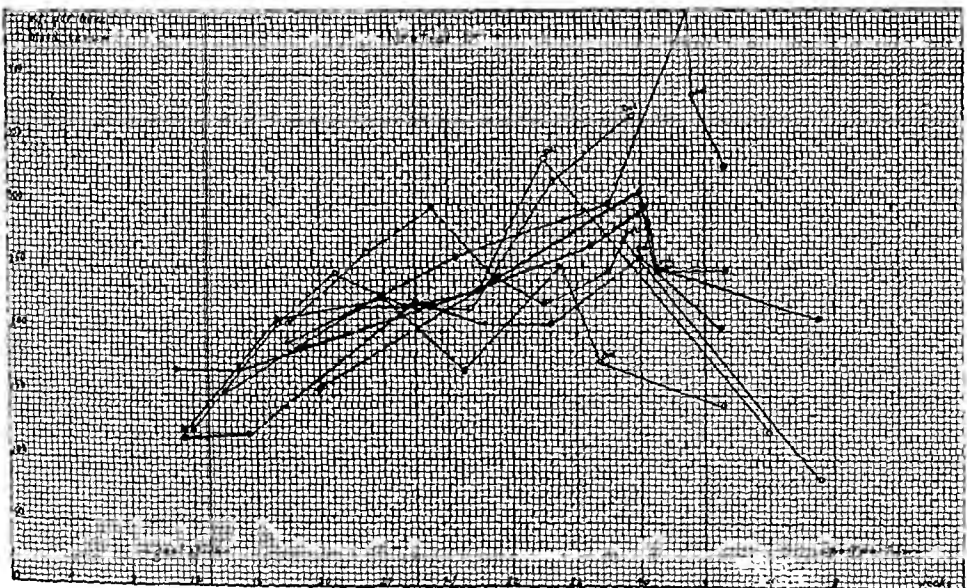


Graph 4.

Boyd<sup>17</sup> records normal plasma neutral fat values of from none to 773 mg. per cent; phospholipid of 21 to 510 mg. per cent; free cholesterol of 5 to 136 mg. per cent. Thus the important information is the curve of value of the various lipids for each subject rather than the individual value of a lipid fraction.



Graph 1.



Graph 2.

In some instances the delivery specimen demonstrated a decreased value over the last previous calculation.

No apparent relation can be attributed to gain in weight, hemoglobin concentration, duration of labor, seminarcosis, or anesthesia.

Neutral fat in 6 of 7 sets of determinations showed the greatest percentage increase in value.

A decrease in all lipid elements was noted frequently, but not constantly, at delivery.

A subsequent report will discuss fetal cord blood serum lipids and blood serum lipids in the puerperium.

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#### DISCUSSION

DR. E. D. PLASS, IOWA CITY, IOWA.—At our last meeting one of the blood lipids, cholesterol, was introduced by Drs. Colvin and Bartholomew into their discussion of the etiology of the toxemias of pregnancy. Their findings indicated that the whole blood of toxemic patients had a higher concentration of total cholesterol than that of normal women at corresponding periods of gestation. They then postulated a cholesterol vascular change as predisposing to the placental infarction, which they believe to be of etiologic significance.

On the other hand, the paper which we have just heard deals only with the changes in the various determinable fat fractions of the blood serum during the course of normal pregnancy. Each of the women studied showed gradual increases in the several lipid constituents up to the time of delivery, even though there was no consistent and significant alteration in the degree of unsaturation of either the phospholipid fatty acids or the total fatty acids. The significance of this lipemia is not clear, but it must be viewed as part of the normal metabolic response to pregnancy.

The liver plays a dominant role in fat metabolism, and the question naturally arises as to whether the detected alterations in the serum lipids during normal pregnancy are consistent with hepatic malfunction, which has long been postulated but never clearly proved. Data concerning the variations in human liver disease unassociated with jaundice are conflicting, but a recent and still unpublished study by Levine indicates that there is a decrease in the unsaturation of the various fatty acids and in both the total and the esterified cholesterol. On the basis of these findings it seems reasonable to conclude that the fat metabolizing ability of the liver is not diminished by pregnancy. Such negative evidence serves to strengthen the belief that deficient hepatic function is not a conspicuous part of the metabolic changes incident to gestation, and that the importance attached to this organ as a possible cause of certain of the complications of pregnancy was unjustified.

DR. JAMES R. BLOSS, HUNTINGTON, W. VA.—I wish to report two additional patients who have shown positive Wassermanns and were also positively hypoendocrine. These two, together with three previously reported, became negative immediately upon the change of the lochia. All five of the babies of these patients were negative, both from the cord and from blood taken from their heels. I cannot explain this phenomenon other than by some change in the blood cholesterol of these hypoendocrine patients.

There is a rise in phospholipid similar in percentage to that of cholesterol.

The phospholipid : total cholesterol ratio is of special interest because of the antagonistic behavior of these two elements as observed in several biologic processes. No consistent change in this ratio is noted with the progress of pregnancy.

Phospholipid fatty acid iodine numbers and total fatty acid iodine numbers, indices to the degree of unsaturation of these respective factors, show some variations. These changes are not within any range as to warrant a conclusion as to any degree of change in saturation of the fatty acids. The ratio of total fatty acids: phospholipid has been considered to be of general importance in lipid metabolism because of the relation between these two factors during fat absorption.

#### DISCUSSION

The results discussed at this time are in the nature of a preliminary report. The changes in blood serum lipid concentration from early pregnancy to term are reported. Findings in fetal cord blood serum and in the puerperium will be recorded at a subsequent time.

The close organic relationship of certain members of the lipid group to substances which are of great significance in obstetrics and gynecology is recognized. The organic structure of cholesterol is closely related to that of the estrogens, progesterone, and ergosterol. Phospholipid and cholesterol balance is one to warrant close consideration. The antagonism of these two lipids is extremely interesting and may play an important role in obstetrics. The hydrophilic and hydrophobic properties of these two substances have not been considered extensively by the clinician (Sinclair<sup>18</sup>).

Boyd<sup>17</sup> notes that human plasma contains about the same amount of fatty substances as it does of inorganic salts and much more lipid than of water-soluble organic compounds such as the nitrogenous derivatives and glucose. The lipids of plasma are exceeded only by the albumins and globulins in amount present and are about equal in concentration to that of fibrinogen.

The relation of this relatively large concentration of lipids to colloidal osmotic pressure of plasma and to the genesis of edema warrants further study.

#### CONCLUSIONS

Blood serum lipids were studied at frequent intervals in a series of normal women from early pregnancy through parturition and in the puerperium.

A lipemia is noted in pregnancy. It is characterized by a most marked increase in neutral fat and a lesser increment in cholesterol fractions and phospholipid.

The rise in lipid content is gradual through gestation.

No significant changes in unsaturation of the phospholipid fatty acids or total fatty acids were noted.

The ester cholesterol: total cholesterol ratio remains remarkably constant throughout pregnancy.

The phospholipid: total cholesterol ratio exhibited was quite variable but no constant change was noted.

No apparent relation of weight gain, weight of the baby, hemoconcentration, seminarcoosis, or anesthesia was noted.

At the present time there have been classified by the method described 294 vaginal and vulval strains; 68 as previously reported,<sup>16</sup> 75 isolated from patients with symptoms of mycotic vulvovaginitis (unpublished), and 151 strains which form the material for this report.

In previous studies,<sup>13, 16</sup> no effort was made to correlate the patient's history and the clinical findings with the occurrence of yeastlike fungi in the vagina. The present study was undertaken to determine in a series of 200 pregnant patients, (1) the incidence of yeastlike fungi on the vulva as compared to the incidence in the vagina; (2) the relation of the patient's symptoms and the findings on vulval and vaginal examination to the species of yeastlike fungi isolated from the vulva and vagina; (3) the possibility of any degree of correlation existing between the presence of agglutinins in the patient's serum, skin sensitivity, and positive cultures; (4) the incidence of trichomonads in patients with yeastlike fungi; and (5) the relation of the vaginal smear types to the presence of yeastlike fungi or trichomonads.

### HISTORICAL

According to Castellani,<sup>1</sup> Wilkinson in 1840 (Lancet 1: 1840) was the first to report yeastlike organisms in the vaginal discharge. Few attempts were made, however, to study any number of vaginal strains until 1924 when Castellani and Taylor<sup>3</sup> described vaginal *Monilia* and vaginal moniliases. Plass, Hesselstine, and Borts<sup>5</sup> in 1931 found *Monilia* in 12 of 18 pregnant patients who had vaginal irritation, a percentage of 66.7. In a control group of 46 pregnant women without symptoms, *Monilia* were demonstrated in 15 patients, 32.6 per cent. These authors also found that monilia vaginitis in pregnancy was a definite source of infection with oral thrush of the newborn. Bland and others,<sup>15</sup> 1937, found pregnancy to be a predisposing factor in the production of mycotic vulvovaginitis. By vaginal inoculations with strains of *Monilia* from patients with varying degrees of symptoms, they were able to infect pregnant women in a higher percentage of instances than they were able to infect the nonpregnant women. These investigators also noted that experimental inoculation was least successful in patients with profuse discharge. This observation is interesting to us, because in our own series many of the patients from whom both *Monilia* and trichomonads were recovered were diagnosed clinically trichomoniasis prior to the establishment of the diagnosis by the routine outlined in this study.

Studies of the vaginal monilias have also been made by Popoff, Ford and Cadmus,<sup>4</sup> 1929, by Hesselstine,<sup>7</sup> 1933, by Hopkins and Hesselstine,<sup>11, 12</sup> 1936, and by Weinstein and Wickerham,<sup>19</sup> 1938.

### MATERIAL

The race, marital status, parity, and the duration of pregnancy of the patients studied are shown in Table I. The 54 white patients were unmarried and confined to a maternity home. The 146 colored patients were regularly attending the outpatient prenatal clinic. Most of the patients were of a low economic status. The only criterion used in the selection of the patients for study was no past history or complaint of pruritus, discharge, or irritation prior to pregnancy. The patients with these complaints were excluded from the series.

### METHOD OF STUDY

*History.*—A special mimeographed history sheet was used throughout the study. The same questions were asked each patient. No leading questions were asked. No effort was made in taking the patient's history to differentiate degrees of pruritus, discharge, or irritation. The patient was simply asked if itching had been experienced or discharge had increased with pregnancy, or if irritation was or had been present. Whereas the inadequacy of this method is realized, only in this manner did we feel that we could get comparable results.



DR. JAMES E. DAVIS, ANN ARBOR, MICH.—May I ask Dr. Soule if any check has been made upon the lipid level and the gonadotropic levels in the patients he has studied? In pregnancy there is normally an increase of anabolic activity, and there is a very great difference in the constitutional reaction of different individuals to pregnancy. The lipoids and the cholesterol are increased, and generally the gonadotropic level is also increased. In thyroid hypofunction and pituitary hyperfunction, the blood lipoids are changed.

DR. SOULE (closing).—Basal metabolisms were run on two of these eight patients and were normal.

There is a great possibility that there is some such relationship between the gonadotropic hormones and lipids. There is also a close relationship of certain members of the lipid group organically. Cholesterol and progesterone, estrin and ergosterol, are all closely related structurally.

Phospholipids and cholesterol balances also require close observation. The hydrophilic and hydrophobic properties of these substances have not been studied enough by the clinician. The relation of this relatively large concentration of lipids to colloidal osmotic pressure of plasma and to the tendency to edema is another problem which warrants further study.

## VULVOVAGINAL MYCOSES IN PREGNANCY\*

WITH THE RELATION OF SYMPTOMS TO GENERA AND SPECIES OF FUNGI

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PREGNANCY as a predisposing factor in the occurrence of yeastlike fungi in the vagina and on the vulva is becoming generally well recognized. Carter and Jones<sup>13</sup> in 1937 studied the vaginal flora of 114 apparently normal pregnant patients and of 100 apparently normal gynecologic patients. Yeastlike fungi were isolated from 32 per cent of the 114 pregnant patients and from 14 per cent of the 100 gynecologic patients.

Much of the confusion regarding mycotic vulvovaginitis is due to the inability to identify the genera and species of yeastlike fungi isolated from the vagina and vulva. Lack of systematic methods of study and classification and the fact that yeastlike fungi are frequently isolated from apparently normal vulvas and vaginas have added to the existing confusion. Jones and Martin<sup>16</sup> and Martin, Jones, Yao, and Lee<sup>14</sup> published a method of classifying yeastlike fungi isolated from the vagina. This method of classification was based upon the study of 68 freshly isolated vaginal strains. All of the strains were classified as belonging to the genus *Cryptococcus* or to 1 of 5 species of *Monilia*,† including a new and previously undescribed species, *Monilia stellatoidea*.

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†The generic name *Monilia* is not the correct name for the mycelial forming, non-ascosporogenous yeastlike fungi. It has been used in this paper in preference to any of the several generic names that have been applied to this group. Recent papers by Langron and Guerra, Didders and Lodder, and Ciferri and Redaelli show a tendency to adopt a single generic name for these fungi and it is hoped that some agreement may be reached and terms universally adopted.



**Agglutinations.**—From one-half of the 200 patients in the series, blood was drawn from the median basilic vein, allowed to clot, the serum removed, and used for agglutinations. Antigen was prepared from stock strains of the 5 species of *Monilia* isolated previously from the vagina by one of us (C. P. J.). The antigen was prepared by washing off into saline the twenty-four-hour growth of the fungus on Sabouraud's agar. The saline suspensions of the fungus were precipitated by centrifugation in Hopkin's vaccine tubes. Dilution of the antigen was 1:1000 by volume of packed cells. The method of agglutinations consisted in shaking for thirty minutes in a mechanical shaking machine, placing in the refrigerator over night, and reshaking for thirty minutes before reading.

**Intradermal Tests.**—One hundred of the 200 patients in the series were tested for skin sensitivity to antigens prepared from stock strains of the 5 species of vaginal *Monilia*. Antigen for intradermal testing was prepared in the same manner as antigen used for agglutinations, with the exception that the fungi were heat killed, and 0.35 per cent tricresol was added as a preservative. For testing, 0.1 c.c. of each of the 5 antigens was injected intradermally in the forearm. Readings of the intradermal tests were made in twenty-four to forty-eight hours.

**Classification of the Fungi.**—Detailed methods of classification of the yeastlike fungi have been described previously by Jones and Martin,<sup>16</sup> 1938, and Martin, Jones, Yao and Lee,<sup>14</sup> 1937.

After growth on Sabouraud's agar, yeastlike colonies were picked and inoculated into Sabouraud's broth. After forty-eight hours the broth was shaken and streaked on beef extract blood agar plates. From the blood agar plates only the smooth typical colonies were selected for study. Rough or variant colonies were considered the result either of contamination by bacteria, or of complete or partial dissociation and not within the scope of this report. The method as previously described consisted of observation of the growth in Sabouraud's broth at forty-eight hours, study of colony characteristics on beef extract blood agar, carbohydrate fermentations, observations of morphology on corn meal agar, the production of ascospores on carrot plugs and rabbit pathogenicity tests.

## RESULTS

**Incidence.**—Yeastlike fungi belonging to either the genus *Monilia*, *Saccharomyces* or *Cryptococcus* were isolated from 86, or 43 per cent, of the 200 patients studied. Eleven, or 20.4 per cent, of the 54 white patients and 75, or 51.4 per cent, of the 146 colored patients showed positive cultures from either the vagina or labia, or both. If positive labial cultures are disregarded, 66, or 33 per cent, of the patients had positive vaginal cultures.

Vaginal and labial cultures showed the same fungus in 62 patients. Four patients had positive vaginal cultures with negative labial cultures. Cultures of the external genitalia were positive in 21 patients in whom no fungi were recovered from the vagina. In 2 patients 2 distinct species of yeastlike fungi were cultured from the labial folds.

Our inability to recover several species of yeastlike fungi from a larger number of patients was probably due to the similarity of the colonies of the different species on Sabouraud's agar.

**Classification.**—The carbohydrate fermentations of the 124 strains classed as of the genus *Monilia* are shown in Table II. In Table III the carbohydrate fermentations of the strains classed as *Cryptococci* and *Saccharomyces* are shown.

As in a previous report, Jones and Martin,<sup>16</sup> the majority of the strains belonged to the species *Monilia stellatoidea*. The second largest group was *Monilia albicans*. Twenty-seven of the strains isolated belonged to the genera *Saccharomyces* and *Cryptococcus*.

**Rabbit Pathogenicity Tests.**—Each strain identified as *M. albicans* was tested for pathogenicity when inoculated intravenously into rabbits. The method described by Benham<sup>6</sup> and Stovall and Pessin<sup>8</sup> was used. For intravenous injection 1 c.c. of a 1 per cent saline suspension of the organisms was used. In each rabbit, death occurred in from one to five days. In the rabbits which survived for as long as two or three days, macroscopic lesions were demonstrable in the kidneys and in

TABLE I

RACE	WHITE	NUMBER
	COLORED	54
Age	10-19	146
	20-29	93
	30-39	82
	40-49	23
Marital	Married	2
	Single	112
Approximate month of pregnancy	2-3	88
	3-4	2
	4-5	11
	5-6	10
	6-7	34
	7-8	59
Parity	Primiparas	84
	Multiparas	83
		117

*Vaginal Examination.*—The impression from the character of the discharge, vaginal mucosa, cervix, etc., was recorded without knowledge of the cultural or hanging drop findings. The impression from the vaginal examination was limited to one or more of four things: mycotic vulvovaginitis, trichomoniasis, cervicitis, or negative findings. A diagnosis of mycotic vulvovaginitis from the vaginal examination meant, white, flaky or cheesy discharge, thrushlike patches, etc.; of trichomoniasis, frothy, bubbly or purulent discharge, or the presence of punctate red spots on the cervix or vaginal mucosa, said to be characteristic of the condition. Doubtful patients were classed as negative. Patients thought to be within normal limits were classed as negative.

*Vaginal Cultures.*—Cultures from the vagina were taken at the time of the vaginal examination. After the insertion of a sterile unlubricated speculum, a swab was used to collect any suspicious material from the vaginal walls, posterior fornix or cervix. Immediately after collection, the collected material from the swab was planted on a Sabouraud's agar slant and was grown at room temperature.

*Labial Cultures.*—All of the labial cultures were collected on swabs moistened with Sabouraud's broth. At the time of collection the swabs were removed from the broth, and cultures were taken from between the labial folds and around the vulva. The swabs were then reinserted into the broth and the culture grown for twenty-four hours at room temperature before plating on Sabouraud's agar plates.

*Fresh Preparation for Trichomonads and Yeasts.*—Two vaginal swabs were placed in 1 c.c. of normal saline and fresh preparations were examined immediately for the presence of yeastlike organisms or trichomonads. The time consumed in the examination of the fresh preparation was not prolonged and represented on the average four or five minutes.

*Smears.*—Smears were made of the vaginal discharge of each patient and stained with Gram's stain. Each smear was classified into 1 of 3 types as previously described by Carter and Jones,<sup>13</sup> 1937, a slight modification of the method first described by Schroder,<sup>2</sup> 1921.

Type 1. Vaginal bacilli alone or vaginal bacilli with yeasts.

Type 2. Vaginal bacilli with other organisms.

Type 3. No vaginal bacilli.

Whereas it is realized that certain objections to this method are valid, we do feel that with some experience one may predict from the study of vaginal smears the predominant types of organisms which might be encountered if complete cultures were done.

Any evaluation of pruritus, discharge, or irritation, must of necessity include consideration of trichomonads and of bacterial infections. Although patients in this series complained of both pruritus and discharge when neither fungi nor trichomonads could be recovered from the vagina, only yeastlike fungi and the protozoa will be considered etiologic agents in this report. Many patients were diagnosed from the character of the discharge as having trichomoniasis when trichomonads were not found in the hanging drop. This finding lends some support to the idea that certain bacteria may produce a vaginitis which cannot be differentiated clinically from that caused by trichomonads. A more complete report on trichomoniasis of pregnancy is to be published later.

*Monilia albicans*.—Ten (50 per cent) of the 20 patients with positive vaginal or labial cultures for *M. albicans* complained of pruritus. Seven of the 10 showed both trichomonads and *Monilia*. A diagnosis of mycotic vulvovaginitis from the vaginal examination was recorded in only 4 of the 20 patients with positive cultures; 3 of the 4 complained of pruritus.

TABLE IV

		MONILIA	
		ALBICANS	STELLATOIDEA
		NUMBER	
Incidence	Patients with positive cultures	20	38
	Positive vaginal cultures	17	35
	Positive labial cultures	20	35
	Positive labia and vagina	17	32
Fresh preparation	Trichomonads	10	24
	Yeast	8	16
History	Itching	10	15
	Discharge	13	17
	Irritation	2	0
Impression from the vaginal examination	Trichomoniasis	8	14
	Mycotic	4	11
	Cervicitis	7	8
	Negative	5	14

*Monilia stellatoidea*.—The number of patients with pruritus in the 38 from whom *Monilia stellatoidea* was cultured was 15, or 39.4 per cent. Twelve of the 15 patients with pruritus showed trichomonads in addition to the fungus. That is, a multiple infection occurred in all but 3 of the patients complaining of pruritus. Seventeen of the 38 patients complained of increased discharge; 10 of the 17 were in the group complaining also of pruritus. A diagnosis of mycotic infection from the vaginal examination was made in 3 patients, of moniliasis plus trichomoniasis in 4 patients. Three patients who complained of neither pruritus nor discharge were diagnosed from the vaginal examination as mycotic infections.

*M. (parasitosis) parakrusei*,\* *M. (candida) tropicalis*\* and *M. Krusei*.—*M. (parasitosis) parakrusei*: Of 7 patients with positive cultures, in only 1 was the fungus recovered from the vagina. In this patient there was no complaint of pruritus or discharge. Two of the 7 patients were diagnosed as trichomoniasis and the diagnosis was confirmed by hanging drop. In no patient was a diagnosis of mycotic infection justified from the patient's history or the vaginal findings.

\*Since the work of Martin, Jones, Yao and Lee in which 6 species of *Monilia* were described, Langeron and Guerra have shown that the species *candida* and *tropicalis* are identical and have adopted *tropicalis* as the species name. Likewise *parasitosis* and *parakrusei* were found to be identical and the species name *parakrusei* is to be preferred. Therefore *Monilia candida* should become *Monilia tropicalis* and *Monilia parasitosis* should become *Monilia parakrusei*.

TABLE II. MONILIA FERMENTATIONS

	NUMBER OF STRAINS	DEX- TROSE	SAC- CHAROSE	LACTOSE	MALTOSE	RABBIT PATHOGE- NICITY
<i>Stellatoidea</i> vagina	35	AG*	-	-	AG	-
<i>Stellatoidea</i> labia	35	AG	-	-	AG	-
<i>Albicans</i> vagina	17	AG	A	-	AG	+
<i>Albicans</i> labia	20	AG	A	-	AG	+
<i>Candida</i> vagina	2	AG	AG	-	AG	Not done
<i>Candida</i> labia	1	AG	AG	-	AG	Not done
<i>Krusei</i> vagina	2	AG	-	-	-	Not done
<i>Krusei</i> labia	4	AG	-	-	-	Not done
<i>Parasilosis</i> vagina	1	AG	-	-	-	Not done
<i>Parasilosis</i> labia	7	AG	-	-	-	Not done
Totals	124					

\*AG, Acid and gas. A, Acid. -, Negative.

TABLE III. GENUS SACCHAROMYCES AND CRYPTOCOCCUS

	NUMBER OF STRAINS	DEXTROSE	SAC- CHAROSE	LACTOSE	MALTOSE
<i>Saccharomyces</i> vagina	1	AG*	AG	-	-
<i>Saccharomyces</i> labia	1	AG	AG	-	-
<i>Saccharomyces</i> vagina	1	AG	AG	-	AG
<i>Saccharomyces</i> labia	1	AG	AG	-	AG
<i>Cryptococcus</i> vagina	3	AG	-	-	-
<i>Cryptococcus</i> labia	3	AG	-	-	-
<i>Cryptococcus</i> vagina	2	A	-	-	-
<i>Cryptococcus</i> labia	5	-	-	-	-
<i>Cryptococcus</i> vagina	2	AG	AG	-	AG
<i>Cryptococcus</i> labia	4	AG	AG	-	AG
<i>Cryptococcus</i> vagina	1	AG	AG	AG	-
<i>Cryptococcus</i> labia	1	AG	AG	AG	-
<i>Cryptococcus</i> vagina	1	AG	AG	-	-
<i>Cryptococcus</i> labia	1	AG	AG	-	-
Total	27				

\*AG, Acid and gas. A, Acid. -, Negative.

many rabbits in other organs. On injection of the more highly pathogenic strains, many rabbits failed to survive this length of time and in these animals the fungi could be cultured from the kidneys.

Each strain identified as *M. stellatoidea* was tested by the intravenous injection in rabbits of 2 c.c. of a 1 per cent suspension (this dose was twice the lethal dose used for *M. albicans*). In no rabbits did death occur.

#### RELATION OF SYMPTOMS AND VAGINAL FINDINGS TO THE GENERA AND SPECIES OF FUNGI

The incidence of the various genera and species of yeastlike fungi, the findings in the fresh preparations in that group of patients, the patients' histories regarding itching, discharge and irritation, and the impression from the vaginal examinations are shown in Tables IV, V, and VI. The findings in each group will be discussed separately. In our experience the predominant symptom of mycotic vulvovaginitis is pruritus. Patients with uncomplicated mycotic vulvovaginal infections rarely complain of excessive discharge. However, multiple infections are common and this is especially true in the colored pregnant females.

Further work must be done to determine, if any, the role played by *Cryptococci* in the production of vaginal pathologic change.

### GENUS SACCHAROMYCES

True ascosporeogenous yeastlike fungi from the standpoint of vaginal pathology are relatively unimportant. Though the patients reported here are insufficient for drawing conclusions, the rarity of this type of fungus in the vagina is proved by the fact that of several hundred strains isolated from the vagina in our clinic, only in 4 strains were we able to prove the formation of asci. These 4 strains were isolated from 2 patients. In neither patient were we able to suspect the presence of the fungus from the symptoms of the patient or from the vaginal examination.

*Saccharomyces* belong to the group of commercially important yeasts and are of no, or at least of minor, importance in medical mycology. Their importance is assumed because of the necessity of differentiation from the nonascosporeogenous *Monilia* and *Cryptococci*.

### RESULTS OF THE INTRADERMAL TESTS

Forty-nine of the 100 patients tested showed some degree of reaction to 1 or more of the 5 antigens used.

Of the 49 patients with positive intradermal tests, 15, or 30.6 per cent, were positive by culture for fungi belonging to the genus *Monilia*. In 12 of the 15 patients with positive intradermal tests and cultures, the species of *Monilia* isolated corresponded to the patient's skin tests. In most of these patients, however, positive intradermal tests were obtained with other species of *Monilia*.

Of the 51 patients with negative intradermal tests, *Monilia* were isolated from either the vagina or labia or both in 19, or 37.3 per cent.

TABLE VII. TWENTY-FOUR-HOUR SKIN TEST REACTIONS TO 5 SPECIES OF *MONILIA*

AREA OF ERYTHEMA	ALBICANS	STEL-LATOIDEA	CANDIDA	KRUSEI	PARASILOSIS
Less than 1 cm.	16	19	7	3	3
1 cm.-2 cm.	22	17	4	2	0
2 cm.-3 cm.	7	6	0	0	0
3 cm.-4 cm.	1	2	1	0	0
Totals	46	44	12	5	3

The percentage of patients harboring *Monilia* either in the vagina or on the labia was higher in the group of patients with negative intradermal tests than in the group with positive tests.

The twenty-four-hour skin test reactions are shown in Table VII.

### RESULTS OF AGGLUTINATIONS

The results of the agglutinations with the serum titers are shown in Table VIII. Thirty-five of the 100 patients whose sera were tested against the stock strains of the 5 species of *Monilia* showed agglutinins to 1 or more species. The highest and lowest titers recorded were 1:80 and 1:5, respectively.

TABLE VIII. POSITIVE AGGLUTINATION TESTS WITH SERUM TITERS

SERUM DILUTIONS	ALBICANS	STEL-LATOIDEA	CANDIDA	KRUSEI	PARASILOSIS
1:5	7	8	3	0	1
1:10	13	12	15	1	2
1:20	4	7	4	1	0
1:40	1	2	2	0	0
1:80	2	1	0	0	0
Totals	27	30	24	2	3

TABLE V

		MONILIA		
		PARA-SILOSIOS	CANDIDA	KRUSEI
		NUMBER		
Incidence	Patients with positive cultures	7	2	4
	Positive vaginal cultures	1	2	2
	Positive labial cultures	7	1	4
	Positive labia and vagina	1	1	2
Fresh preparation	Trichomonads	2	1	1
	Yeast	0	2	1
History	Itching	0	1	0
	Discharge	4	0	2
	Irritation	0	0	0
Impression from the vaginal examination	Trichomoniasis	2	0	0
	Mycotic	0	1	0
	Cervicitis	2	0	0
	Negative	3	1	0

*M. (candida) tropicalis*: Of the 2 patients with positive cultures for *M. (candida) tropicalis*, 1 complained of pruritus and the impression from the vaginal examination was mycotic vulvovaginitis. The second patient had no complaint and the impression was negative. *M. Krusei*: Of the 4 patients positive for *M. Krusei*, 2 were positive from the labia only and 2 from the labia and vagina. None of the 4 patients complained of pruritus, and all were diagnosed from the vaginal examination as negative.

#### ✱ GENUS CRYPTOCOCCUS

Of 14 patients with positive cultures for the simple yeastlike organisms belonging to the genus *Cryptococcus*, only 7 were positive in both the vaginal and labial cultures and 7 from the labia only. Of the 14 patients 2 complained of pruritus vulvae. In 1 patient with pruritus, *M. albicans* and trichomonads were both present in addition to the *Cryptococcus*. The second patient with pruritus also had trichomonads. In none of the 14 patients did the vaginal examination show evidence of a mycotic infection. In only 1 patient were the fungi demonstrable without culture.

The outstanding clinical finding in these patients was some degree of cervicitis in 8 of the 14. That the fungi were related in any way to the cervicitis is doubtful. Benham<sup>9</sup> and others have shown that *Cryptococci* occur frequently on the normal skin, around the nails, etc.

TABLE VI

		GENUS	
		SACCHAROMYCES	CRYPTOCOCCUS
		NUMBER	
Incidence	Patients with positive cultures	2	14
	Positive vaginal cultures	2	7
	Positive labial cultures	2	7
	Positive labia and vagina	2	7
Fresh preparation	Trichomonads	0	4
	Yeast	0	1
History	Itching	0	2
	Discharge	0	6
	Irritation	0	0
Impression from the vaginal examination	Trichomoniasis	0	3
	Mycotic	0	0
	Cervicitis	1	8
	Negative	1	5

ists, of the vagina must be established before too much significance can be attached to the findings of unidentified yeastlike fungi by culture. Any evaluation of therapeutic methods of treatment must of necessity be based upon the complete identification of the species of fungus involved as well as the symptoms of the patient.

In interpreting the results of this study, it must be kept in mind that the 200 patients in the series represented the types of individuals usually seen in the outpatient clinic, seeking prenatal care. If the patients had complained previously of pruritus, discharge, or irritation, they were excluded from the series. As a consequence the symptoms in most of the patients were of a mild nature.

The high incidence of trichomonads in the patients with positive cultures for yeastlike organisms often made the interpretation of the patients' histories and vaginal findings difficult from the mycologic standpoint. Although no definite statements can be made as to the relative pathogenicity of the different genera and species, without considering the resistance of the individual and certain predisposing factors such as diabetes, it is interesting that symptoms of otherwise unexplained pruritus were confined to the groups harboring 3 species of *Monilia*: *albicans*, *stellatoidea* and *candida*.

An examination of the tables shows that of the 86 patients with positive cultures for yeastlike fungi the impression of mycotic vulvovaginitis was listed only 16 times; that fresh preparations were positive for yeastlike fungi prior to culture in 28 patients. This would indicate that all patients with unexplained pruritus, regardless of the findings on the vaginal examination, should be cultured for yeastlike organisms.

No explanation is offered for the high incidence of the new species, *Monilia stellatoidea*, in the pregnant group of patients in contrast to the low incidence of this species of *Monilia* in gynecologic patients with a chief complaint of severe mycotic vulvovaginitis (unpublished data). This present report, however, has only confirmed our earlier belief that *M. stellatoidea*, although closely related to *M. albicans*, deserves species recognition.

In the 16 patients with positive cultures for yeastlike organisms, belonging to the genera *Saccharomyces* and *Cryptococcus*, a diagnosis of mycotic infection from the vaginal examination was not recorded. Only 2 of the patients in this group complained of pruritus; one of these patients had trichomonads and *M. albicans* in addition to the *Cryptococcus*, and the second patient had trichomonads. It is doubtful that *Cryptococci* or *Saccharomyces* will produce vaginal or vulval symptoms except under unusual conditions.

Skin tests as a diagnostic measure are of no value. It is our feeling that in the gynecologic or obstetric patient complaining of marked symptoms of mycotic vulvovaginitis, a markedly positive skin test means a marked sensitivity and some relief may be obtained by desensitization. Desensitization, however, does not eradicate the fungus.

Agglutinations are of little significance in mycotic vulvovaginitis. This fact is to be expected because of the high prevalence of *Monilia* in sputum, stools, etc.

Of the 35 patients whose sera showed agglutinins, positive cultures for *Monilia* were obtained from 12, or 34.4 per cent.

Of the 65 patients with no agglutinins 22, or 33.8 per cent, were positive by culture for *Monilia*.

The presence or absence of agglutinins in the patient's serum could not be used as an index of vaginal or labial infection.

#### THE RELATIONSHIP OF THE PRESENCE OF MONILIA AND TRICHOMONADS TO SMEAR TYPE

*Monilia* were cultured more frequently from patients with Type 2 smears. As was expected the majority of the patients with trichomoniasis showed no Döderlein bacilli by smear and belonged to the Type 3 Group. However, it is interesting to note the occurrence of trichomonads in 9 patients whose smear showed only gram-positive rods of Döderlein's type. This is contrary to the general belief and is in line with recent work by Weinstein,<sup>18</sup> 1938, on the relation of Döderlein's bacillus to vaginal acidity. It is our belief from personal observations, that Neisserian organisms as well as trichomonads occur in a small percentage of patients with smears showing Döderlein's or related bacilli as the only other organisms present. Some doubt is cast on the protective ability of the acidophilus group of vaginal bacilli.

TABLE IX

	TYPE 1 SMEAR 63 PATIENTS		TYPE 2 SMEAR 38 PATIENTS		TYPE 3 SMEAR 99 PATIENTS	
	TRICHO- MONADS	MONILIA	TRICHO- MONADS	MONILIA	TRICHO- MONADS	MONILIA
NO.	9	11	13	15	59	31
%	14.3	17.5	34.2	39.5	59.5	31.3

The smear groupings of the 200 patients, with the incidence of trichomonads and *Monilia*, are shown in Table IX.

#### THE COMPARISON OF CULTURAL, FRESH PREPARATION, AND SMEAR METHODS OF DETECTION OF YEASTLIKE FUNGI

The use of cultural methods for the detection of yeastlike fungi from the vagina was superior to either the examination of fresh preparations or smears. Sixty-six patients were positive by culture. In 28 of these patients, the fungi were demonstrable by examining fresh preparations and in 23 patients by stained smears. As a general rule in patients with a severe mycotic vulvovaginitis, the fungi can be demonstrated without culture. In carriers or patients with a mild infection, cultures are usually necessary.

#### DISCUSSION

Obviously little progress can be made in the study of fungus infections of the vulva and vagina until systematic methods of study and classification are adopted. Much of the confusion existing is due to the large number of asymptomatic carriers. Especially is this true of the pregnant female. Furthermore the normal mycologic flora, if such ex-



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## DISCUSSION

DR. P. BROOKE BLAND, PHILADELPHIA, PA.—We all have been impressed by the high percentage of yeastlike organisms Dr. Carter and his associates recovered by cultural methods. However, in a study of a large group of patients in our clinic, the findings were strikingly similar. In our investigation, comprising an analysis of the vaginal secretions of 1,200 consecutive patients, we discovered yeastlike fungi in 362, or 31.6 per cent.

One should not, however, make a diagnosis of vaginal mycosis on the basis of a positive culture alone. As has been already indicated, many patients may harbor a few of the organisms in the vaginal tract without exhibiting any symptoms or signs of the disease, even over long periods of observation. When by some alteration in nature's method of fungistasis, environmental conditions become favorable for the propagation of the parasites, clinical phenomena supervene.

For the confirmation of clinical infection, Rakoff prefers wet or Gram stained smears. By this method of investigation he was able to confirm the clinical diagnosis in 181, or 15.1 per cent, of our series of patients. In the great majority of these patients, there were present definite clinical signs of the disease. At this point it might be of some importance to mention that in nonpregnant women, our incidence of positive cultures was only 10 per cent and of clinical infection only 2 per cent.

In his study of the various types of mycobacteria Dr. Carter refers, of course, to the common saccharomyces, and he, I presume, includes the different sub-varieties. In this connection I thought it might be of some interest to mention a form we have frequently met with in our work commonly known as the endomyces, a genus characterized by segmented mycelia. For example, in a study of 327 cultures for the presence of mycelia and asci we found endomyces in 12, or 3.2 per cent. The incidence of the other genera was as follows:

<i>Monilia</i>	332	89.5 per cent
<i>Cryptococcus</i>	20	5.4 per cent
<i>Saccharomyces</i>	6	1.7 per cent

Like most other workers who have attempted the species differentiation of *Monilia*, we have been disappointed in the available methods of study and the results obtained thereby. We are particularly anxious to investigate the new species described as *Monilia stellatoidea*. The low pathogenicity of this strain for rabbits as compared with *Monilia albicans* is noteworthy. In our experience, the pathogenicity of any strain of *Monilia* for rabbits was not definitely related to the pathogenicity of the organisms for human beings, as confirmed by experimental inoculations. It is the vaginal environment, especially the quantity of glycogen present, which appears to be the essential factor.

An examination of the table, regarding the relation of *Monilia* and trichomonads to the types of bacteria as determined by smear, shows that yeastlike organisms occur in rather high percentages regardless of smear type. Trichomonads occur with greater frequency in patients whose smears show the absence of Döderlein's bacillus or in the Type 3 group. Although none of the patients was diagnosed clinically as trichomoniasis, 9 in the Type 1 group showed trichomonads.

#### SUMMARY

1. Cultures of yeastlike fungi from the vaginas and vulvas of 200 pregnant women were positive in 86 (or 43 per cent) of the patients. These fungi belonged to the genera *Monilia*, *Saccharomyces*, or *Cryptococcus*. Sixty-six (33 per cent) of the patients showed positive vaginal cultures; 20 (10 per cent) showed positive labial cultures with negative vaginal cultures.

2. A total of 151 strains of yeastlike fungi were classified according to the method previously described by Jones and Martin. Each strain identified as *M. albicans* was pathogenic for rabbits. Each strain identified as *M. stellatoidea* was nonpathogenic for rabbits.

3. In patients in whom the fungi were identified as belonging to the genera *Saccharomyces* or *Cryptococcus*, no symptoms referable to a mycotic infection were described. Symptoms in patients with positive cultures for yeastlike fungi, belonging to the genus *Monilia*, were found only in those in whom the 3 species, *albicans*, *stellatoidea* and (*candida*) *tropicalis* were isolated. Although the incidence of trichomonads was higher in the patients from whom *M. stellatoidea* was cultured, more patients complained of pruritus in the group from which *M. albicans* was cultured.

4. Intradermal skin test with antigens from the 5 species of *Monilia* showed no correlation between positive cultures and positive intradermal tests. The incidence of *Monilia* was higher in the group with negative skin tests.

5. The presence or absence of agglutinins in the patient's serum could not be used as an index of vaginal or labial infection with *Monilia*.

6. Vaginal smear typing showed that monilia were found more frequently in patients with Type 2 smears; that trichomonads were found more frequently in patients with Type 3 smears.

7. Additional work must be done on the mycologic flora of the vulva and vagina in normal patients and in patients with mycotic vulvovaginitis, before we may understand the relative pathogenicity of the different genera and species of yeastlike fungi and may evaluate methods of diagnosis and treatment.

\*Since this paper went to press it has been agreed at an informal meeting of medical mycologists attending the Third International Congress for Microbiology, September 2 to 9, 1939 in New York City, to substitute the generic term *Candida* for *Monilia*. Although Berkhout's original description of the genus *Candida* will require mending, it was the consensus of opinion of those present that the existing confusion would be greatly clarified if workers in this field would use only one generic term while awaiting official action by the rules committee of the International Botanical Congress. Consequently the generic term *Monilia* should be *Candida*.

In this present report therefore the correct names for the five species of mycelial-forming, nonascosporogenous yeastlike fungi are *Candida albicans*, *Candida stellatoidea*, *Candida tropicalis*, *Candida Krusci* and *Candida parakrusci*.

in cases of moniliasis. We at present are trying to determine whether there may be a local rather than a general sensitivity and are testing the sensitivity of the vaginal mucosa.

There are two practical points I think should be emphasized: One is that the best place to cultivate the *Monilia* is in the middle vagina, where they may have a more acid environment. The second is that the mere determination of the presence of the possible pathogens does not mean that one should limit his therapy to the eradication of that organism.

DR. CARTER (closing).—There have been classified to date 294 vaginal and vulval strains, and we know this classification will stand up under the closest scrutiny. The classification is simple and adequate, and from the classification of the various genera and species, we hope in subsequent work to answer some of the questions concerning response of these infections to various methods of therapy.

We too have tried to find the factor which might explain the difference between the findings in the obstetric patients and the findings in the gynecologic patients. The pH of the vagina has given us much trouble, and we are not satisfied with any method we have tried. At the present time we are working in collaboration with a physicist in an attempt to find an accurate and scientific method of determining the vaginal pH. We, too, have done glycogen stains on biopsy specimens of vaginal mucosa, but have never satisfied ourselves that this glycogen factor might explain the predominance of *Monilia stellatoidea* in the vaginas of the pregnant women. We have injected fungus vaccines into the vaginal mucosa and have biopsied the injected areas to study the type of cellular reaction found. We have cultured the penis of the husband of the patient harboring these *Monilia* in the vaginal canal and rarely can we culture fungus from the penis.

We are still attempting to classify the vaginal streptococci and have met with little success. In our original work on the normal vaginal flora, we found anaerobic streptococci in 48 per cent of the gynecologic patients with normal vaginas, and in 44 per cent of the obstetric patients with normal vaginas. We found gamma streptococci in 39 per cent of the gynecologic patients and in 20 per cent of the obstetric patients; we found alpha streptococci in 9 per cent of the gynecologic patients and 10 per cent of the obstetric patients; we found only 3 strains of beta streptococci in the pregnant series and none in the gynecologic series.

We do find that we can alleviate symptoms by local treatment, but we cannot say that we eradicate the yeastlike fungi from the vulvas or the vaginas. In many patients who show a markedly positive skin test to a vaccine made from the fungi found on their vulvas and in their vaginas, we have found that desensitization by means of the vaccines often leads to a marked improvement of the patient's symptoms. However, we have never been able by vaccine therapy to eradicate the yeastlike fungi from the vulvas or vaginas. We may also state that endocrine therapy has given us no lead as to the possible eradication of yeastlike fungi.

In this report it is interesting to note that symptoms of otherwise unexplained pruritus were confined to the groups harboring 3 species of *Monilia*: *albicans*, *stellatoidea*, and *candida*. Only by careful classification and subsequent accurate follow-up may we increase our knowledge of the various genera and species of the vulval and vaginal fungi and the part these fungi play in producing symptoms. Furthermore it is essential that we know the various genera and species before we may determine the effect of our therapeutic measures.

On the basis of criteria described by Benham, which includes: (1) Morphologic characteristics; (2) growth on various media; (3) carbohydrate fermentation reactions; (4) serologic studies, and (5) pathogenicity, we attempted the identification of 210 strains during the past five years with the following results:

<i>Monilia albicans</i>	143	68.6 per cent
<i>Monilia candida</i>	20	9.5 per cent
<i>Monilia parasitosis</i>	18	8.6 per cent
<i>Monilia krusei</i>	11	5.2 per cent
Unidentified	18	8.6 per cent

We have not been able to satisfy ourselves that species differences according to this method of classification are of clinical significance.

The observations of Dr. Carter and his fellow-workers on the association of trichomonas and monilia emphasizes the importance of always examining fresh, wet smears in addition to stained preparations and cultures. The experienced observer can find almost always both organisms in the wet smear alone. It is also surprising how frequently the presence of a dual infection may be recognized clinically. Where only the fungi are present, the discharge is scanty, quite thick, and of "cottage cheese" or "bread crumb" consistency. The predominant symptom is pruritus. When trichomonads are also present the discharge is more profuse, of a yellowish gray color, and in addition there are small thick masses of "cottage cheese" material suspended in the discharge. The patients complain of both leucorrhea and pruritus.

In our group of patients, the two organisms were found concurrently in 10.4 per cent. On two occasions Vincent's organisms were associated with *Monilia*. In only one instance was the gonococcus associated. Leptothrix occurred in 8.4 per cent of our patients. The presence of leptothrix is mentioned especially because this funguslike organism is not infrequently mistaken by inexperienced workers for the hyphae of monilia.

Döderlein's bacilli were present with *Monilia*, either alone or with other organisms, in 68.2 per cent of the patients. This, we believe, is due probably to the presence of large quantities of glycogen in the vagina during pregnancy and which forms a favorable substratum for both lactobacilli and fungi.

Finally, I should like to inquire whether Dr. Carter and his associates have noted any correlation in the species of *Monilia* in children with oral thrush and the organisms found in the vaginas of infected mothers. Personally, we have been impressed by the high incidence of oral thrush in babies born of infected mothers in the private home where the possibility of contamination from other children is more or less negligible.

DR. A. N. CREADICK, NEW HAVEN, CONN.—In Dr. Weinstein's first published series of 400 cases, 67 yeasts were recovered, and in that series Döderlein's bacillus appeared only with a low pH. Knowing that Dr. Carter was going to discuss this subject, we ran a series of routine cultures on patients presenting themselves to the Gynecological and Obstetrical Dispensary and in a private office, and in 109 cases demonstrated 17 *Monilia*, which we did not differentiate into different strains. There was no correlation between organisms associated with *Monilia*, and there was no correlation of gynecologic conditions and yeasts.

DR. E. D. PLASS, IOWA CITY, IOWA.—I believe as Dr. Creadick pointed out that there must be some change in the physiology of the vagina that makes the *Monilia* pathogenic at times and nonpathogenic at other times. It is well known that both the *Monilia* and the trichomonads may be present without producing symptoms, and we have unpublished evidence that the gonococcus may occasionally be asymptomatic. So the fundamental question concerns the change in the vaginal physiology which suddenly leads to symptomatic manifestations in the course of these infections, or in turn relieves the symptoms of discharge and infection.

As a result of our own independent studies, I completely agree with Dr. Carter that we can obtain very little practical help from either agglutination or skin tests

usually becoming apparent after the fourth month. Also the dilatation becomes most marked around the seventh month, to recede somewhat before delivery. DeLee felt that since the specific gravity of the uterus is the same as that of the other abdominal organs, pressure from the uterus would be impossible. But Williams considered that the uterus caused direct pressure on the ureters. Several have felt that, since catheters can easily be passed up the ureters, obstruction is not present. It would seem to us that the diffuse pressure external to the ureter might collapse atonic ureters and yet this distributed pressure not be noted by the entering catheter.

Some have stated that similar dilatations do not occur with pelvic tumors of similar size. This, however, is refuted by Baker and Lewis,<sup>6</sup> who found such dilatations in 16 cases with pelvic tumors. Hundley and others<sup>1</sup> found agreeing dilatations in 7 of 8 cases with pelvic tumors, with rapid regression after operation. While some authors (Lee and Mengert<sup>7</sup>) have stated that the dilatation is not relieved by indwelling catheters for twenty-four hours, Hundley shows photographs of definite decrease in the hydroureters and hydronephrosis after two to three days.

It has also been postulated that in part, the obstruction may be caused by the general hyperemia of the pelvic tissues at the time of pregnancy.

Considering further the obstruction theories, exclusive of pressure from the uterus and general pelvic hyperemia, Hofbauer's<sup>8</sup> work stands out for its originality. By the examination of 14 autopsy specimens, he demonstrated a definite hypertrophy of the periureteral sheath in the lower ureter near the bladder, consisting of connective tissue and longitudinal muscle fibers. He considered that this hypertrophy and hyperplasia encroached upon the lumen of the lower ureter and was responsible for the urinary obstruction. Several others have confirmed this anatomic finding of Hofbauer's, but are uncertain as to its role in dilatation. Baird<sup>9</sup> states that the amount of hypertrophy and hyperplasia does not always correspond to the degree of dilatation, and that while the dilatation is more marked on the right side, the hypertrophy is the same in both ureters.

In contrast to the theories of obstruction, there are those who believe that atony of the urinary tract is either wholly or in part responsible for the dilatation. Relaxation and atony of the uterus, large bowel and other pelvic structures are rather evident, and similar atony of the urinary tract would not seem unlikely. Traut and McLane<sup>10</sup> by means of the hydrophorograph have shown that diminished peristaltic activity progresses up to the seventh or eighth month, with some definite return of activity in the last month of pregnancy. They feel that this diminished peristaltic activity cannot be explained on a basis of dilatation, because in a few instances very widely dilated ureters were possessed of normal muscular activity, and because of at least a partial return of peristalsis during the ninth month. It would seem that tracings from hydroureters and hydronephroses not related to pregnancy, but of like duration, should be compared to arrive at an accurate opinion. The work of Traut and McLane is exceedingly interesting, highly suggestive, but not conclusive in our opinion. The increase in tone near delivery has also seemed likely to a number of investigators who found a decrease in dilatation in the ninth month by means of intravenous pyelograms. Many writers have spoken vaguely of hormonal action producing atony of the ureters, while others intimate that this should be a known fact. Hundley and associates were unable to produce any changes in ureters of dogs by estrogenic hormone (amniotin). Recently Brack and Langworthy<sup>11</sup> have shown that estrogenic hormone increases the vesical muscle tone in castrated cats. So far as we know, there is no proof that ureteral atony is due to hormonal action.

Our conclusions from the literature of the probable cause of dilatation of the urinary tract in pregnancy are in accord with those of Baird. There is very likely some atony, the cause of which is unknown, possibly

## STUDIES ON THE URINARY TRACT AFTER DELIVERY\*

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THIS study was begun after the occurrence of severe pyelitis in two pregnant patients under our care, followed by slowly diminishing dilatation of the ureters and kidney pelves for nearly two years. This prompted us to inquire when the urinary tract should return to normal after delivery and the variations in such time, and also to study the ureters and kidneys months after an attack of pyelitis of pregnancy. Regarding the first, much could be learned from the literature; but with the latter apparently little work has been done.

There have been many discussions of the dilatation of the ureters and kidney pelves during pregnancy. Several writers<sup>1</sup> have mentioned the early descriptions of Rayer in 1841, and of Cruveilhier in 1843. Opitz in 1905 perhaps first ascribed the dilatation of the urinary tract to pressure from the enlarging uterus. In various early reports of autopsies, dilatations were said to be present in from 25 to 100 per cent of the cases (Carson<sup>2</sup>). In 1925 Kretschmer and Heaney<sup>3</sup> used retrograde pyelography to show dilatation in all of 12 cases of pyelitis and in 16 of 19 normal cases. Since then many studies have been made by means of retrograde and intravenous pyelograms. Duncan and Seng<sup>4</sup> in 1928 studied 78 apparently normal pregnancies with retrograde pyelography, finding some degree of dilatation in every case, more often and more marked on the right side. These findings have been largely confirmed by many investigators, except that very occasional cases may apparently show no dilatation. An excellent review of the large literature has been recently made by Traut and Kuder.<sup>5</sup>

Several causes of dilatation of the urinary tract have been suggested. The most frequently mentioned cause is that of obstruction of the ureters. The enlarging uterus has been considered by many, particularly the earlier workers, as the prime reason for the dilatation, through its direct pressure effect. The fact that the dilatation is almost always above the pelvic brim involving the upper ureter and kidney pelvis lends weight to this theory, while the ureter below the pelvic brim shows little or no dilatation. The right ureter and pelvis may show marked dilatation; and in the left, none. When the dilatation is bilateral, it is as a rule more marked on the right side. This difference is attributed to the sigmoid which may act as a cushion to protect the left ureter, to the anatomy of the iliac arteries which causes a more marked angle in the crossing of the ureter on the right and to the dextro-rotation of the uterus (also perhaps due to the sigmoid), causing more pressure on the right ureter.

The obstruction-from-pressure theory is refuted by the fact that dilatation occasionally occurs in the second month of pregnancy, although

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TABLE I. NORMAL PREGNANCY

CASE	AGE	TIME BEFORE DELIVERY	INTRAVENOUS PYELOGRAM	TIME AFTER DELIVERY	INTRAVENOUS PYELOGRAM
1	18	15 da.	Hydronephrosis, right large	8 da. 3 mo.	Hydronephrosis, right, some larger. Left some larger Hydronephrosis, right as before except better cuppings Left pelvis normal
2	20	34 da.	Hydroureter, bilateral, slight	7 wk. 14 wk.	Normal pyeloureterogram Hydronephrosis, right, slight (aberrant vessel) Hydroureter, left, slight
3	21	28 da.	Normal pyeloureterogram	5 da. 4 wk.	Hydronephrosis, left, moderate Hydroureter, left, slight, marked tortuosity upper third Normal pyeloureterogram
4	20	8 wk.	Hydroureter, left, slight, tortuous	6 da. 11 wk.	Hydroureter, left, slight, somewhat less Normal pyeloureterogram
5	22	5 wk.	Hydronephrosis, right moderate Hydroureter, right, slight Hydronephrosis, left very slight	6 da. 9 wk.	Normal pyeloureterogram Normal pyeloureterogram
6	17	18 da.	Hydronephrosis, right slight. (Little excretion 25 minutes)	9 da. 12 wk.	Hydronephrosis, right slight Hydroureter, right, slight Normal pyelogram (ureters not shown)
7	17	14 da.	Hydronephrosis, right large Hydronephrosis, left, moderately large Hydroureter, left slight (Toxemia unclassified)	3 wk. 7 wk.	Hydronephrosis, right moderately large Hydronephrosis, left, large (more than before delivery) Hydroureter, bilateral moderate Hydronephrosis, bilateral almost as before Ureters not shown
8	18	11 da.	Hydronephrosis, right, moderate Hydroureter, left, moderate	7 da.	Hydronephrosis, bilateral, slight Hydroureter, bilateral, marked
9	19	18 da.	Hydronephrosis, right, moderately large Hydroureter, left, slight	8 da.	Hydronephrosis, right, moderate Hydroureter, right, moderate

of hormonal origin. Superimposed are the above-mentioned physical factors causing obstruction, the most important of which is pressure from the uterus. There may be some hormonal factor increasing the tone of the upper urinary tract immediately before term.

It is of great importance in the follow-up study of any case of pyelitis of pregnancy to know when the physiologic hydroureter and hydronephrosis return to normal.

Duncan and Seng indicate simply that the majority of their cases returned to normal by the ninth day, but that many had not returned to normal by the twenty-fifth day and that some showed dilatation for a long time. Kretschmer, Heaney, and Ockerly,<sup>12</sup> state that of 32 normal cases, 59 per cent returned to normal after two weeks, 34 per cent after six weeks, and 6 per cent after twelve weeks. Lee and Mengert found a definite reduction in dilatation in six to twenty-four hours after delivery and some normal after the third post-partum day. The majority were said to have been normal by the ninth day. Hundley and associates found that of 26 cases, 8 had returned to normal within one week, 5 after two weeks, 12 after six weeks, and 1 after eight weeks.

#### PERSONAL OBSERVATIONS

In our own series of supposedly normal cases, there are 12 to be added to the literature (Table I). These were all primiparas. The ages varied from 17 to 22 years. The urinary histories were negative. The urine showed no pus cells. Intravenous pyelograms, using 20 c.c. of Diodrast\* without reaction, were made in each case as shown in Table I. Attempts were made in each case to have a picture in the ninth month, but the time varies from one day to eight weeks before delivery. Of the 12 cases before delivery, 9 patients showed hydronephrosis on the right, and 3 on the left. The more marked dilatations were found on the right. Three pelves were found normal on the right, and 9 on the left. Hydroureters were found 3 times on the right, and 8 times on the left. This paradox we do not understand. It was of considerable interest that the left ureter was deviated laterally at the pelvic brim in 9 cases from 1½ to 5 cm., while the right was found deviated in only 2 cases. This latter finding has been mentioned by Hundley. One wonders if it might be related to dextrorotation.

In 10 cases intravenous pyelograms were made in less than ten days after delivery (average seven days). Two of these cases had already returned to normal and had shown moderate or moderately large hydronephrosis before delivery. In the remaining 8 cases there was slight reduction in the dilatation in 2, whereas in 2 others there was very definite increase. Frequently the tortuosity of the ureter in its upper third seemed much more marked in the first week after delivery. Two cases, followed eleven and twelve weeks, showed complete return to normal, but had had only slight hydronephrosis and hydroureter previously. Three cases of the more marked dilatations, followed from seven to fourteen weeks, gave no evidence of return to normal. One patient (Case 7) in this series developed an unclassified toxemia, with drowsiness and swelling of hands. Nonprotein nitrogen was 19. Urine, ++ albumin;

\*The Diodrast used in this study was very kindly furnished by the Winthrop Chemical Company.



TABLE II. PYELITIS OF PREGNANCY

CASE	AGE	GRAV- IDA	PYELITIS OF		SIDE	FOLLOW-UP SYMPTOMS	TIME SINCE DELIVERY	FOLLOW-UP PYELOGRAM
			PREG.	PUER- PER.				
1	35	i		+	Rt.	Backache	11 mo.	Hydronephrosis, rt., sl. Hydroureter, rt., sl.
2	25	i	+++		Rt.	None	2 yr.	Hydronephrosis, rt., mod. Hydroureter, rt., sl.
3	39	ii	++++		Rt.	None	16 mo.	Tortuosity left ureter
4	32	i	++++		Rt.	None	17 mo.	Hydronephrosis, rt. mod. Hydronephrosis, lt. sl.
5	31	i		++++	Rt.	None	3 yr. 4 mo.	Hydronephrosis, bil. sl. Small stone lt. kidney
6	29	ii	+++		Rt.	None	13 mo.	Hydroureter, rt., sl.
7	25	i	+++		Rt.	Pain rt. side	5 mo.	Normal pyelouretero- gram
8	23	i	+++		Lt.	Nephro- lithotomy	3 yr.	Hydronephrosis, lt., sl. multiple stones Hydroureter, lt., mod.
9	33	ii	+++		Bil.	Persistent pyuria	2 yr.	Hydronephrosis, bil., marked
10	30	ii		++	Rt.	None sl. pus	8 mo.	Hydronephrosis, rt. marked Hydronephrosis, lt. mod. Hydroureter, bil., mod.
11	24	i	++++		Rt.		5 mo.	Hydronephrosis, rt. marked Hydroureter, rt., mod. Hydroureter, lt., sl.
12		i	+++		Bil.	Malaise	1 yr. 5 mo.	Hydronephrosis, rt., sl. Hydroureter, bil., marked
13	25	i	++		Rt.	Backache unrelieved susp. uter.	4 yr.	Hydronephrosis, rt., mod. Hydroureter, lt., mod.
14	27	i	+++		Rt.	Pain rt. side—pul- monary tubercu- losis	1 yr. 8 mo.	Hydronephrosis, rt., mod. Hydroureter, rt., mod.
15	26	i	++++		Rt.	Recurrent pyelitis	1 yr. 8 mo.	Hydronephrosis, rt., mod. Hydroureter, rt., mod.
16	32	vi		++++	Rt.	Backache	6 yr.	Hydronephrosis, rt., mod. Hydroureter, rt., mod.
17	24	i	++++	+	Bil.	None	2 yr. 1 mo.	Tortuosity lt. ureter Poor excretion dye
18	25	iii	+++ 1st		Rt.	None	6 yr.	Sl. tortuosity rt. ureter
19	25	iii		+++ 3rd	Rt.		4 yr.	Hydronephrosis, rt., mod. Hydronephrosis, lt., sl. Hydroureter, bilat., mod.
20	32	iii	++++ 3rd		Bil.	Now preg. 8 mo.	5 yr.	Hydronephrosis, rt., marked Hydronephrosis, lt., mod. Hydroureter, bilat., mod.
21	39	vii		++ 7th	Lt.		5 yr.	Normal pyelouretero- gram

TABLE I—CONT'D

CASE	AGE	TIME BEFORE DELIVERY	INTRAVENOUS PYELOGRAM	TIME AFTER DELIVERY	INTRAVENOUS PYELOGRAM
10	17	14 da.	Hydronephrosis, right marked Hydronephrosis left, moderate Hydroureter, left, moderate	5 da.	Hydronephrosis, right, slightly less Hydroureter, left, slightly less. (Left kidney normal)
11	22	8 wk.	Hydronephrosis, right, moderately large Hydroureter, left, slight	8 da.	Normal pyelogram
12	18	1 da.	Hydronephrosis right, slight Hydroureter, right, moderate Hydroureter, left, slight	9 da.	Hydronephrosis, right, slight (upper pole) Hydroureter, right, slight

occasional white blood cells. Blood pressure was 150/108 to 130/88. Apparently prompt recovery. It is interesting that this patient had a large hydronephrosis on the right, and moderately large on the left. Seven weeks after delivery there was essentially no change in the pyelograms.

From a consideration of our cases, we do not agree with Lee and Mengert that the majority return to normal by the ninth post-partum day. While it is probably true from the literature that the vast majority of cases return to normal within four to eight weeks and some even within one week, this small series shows three cases with definite abnormalities after seven, twelve, and fourteen weeks. It is even doubtful that these might ever return completely to normal. One (Case 7) of these patients did show some toxemia.

In the literature there are relatively few follow-up studies on women with pyelitis of pregnancy. Corbus and Danforth<sup>13</sup> in 1927 studied 13 cases from two to four weeks after delivery, finding in every case either hydronephrosis, hydroureter, or ureteral stricture. Hofbauer reported the unpublished work of Gardner and Hoerner on 27 patients after from four to thirty-three months. Nine had had puerperal pyelitis and showed on follow-up examination no dilatation or positive cultures. Of the cases with pyelitis before delivery, 8 (44 per cent) later showed marked dilatation of the ureter. These latter patients had had the more severe symptoms.

Dodds reported 124 cases of pyelitis in which the patients were followed up for a considerable period of time, noting symptoms, urine examinations, and cultures. Apparently few x-ray pictures were made. She concluded that of 84 antenatal cases, 49 per cent were cured (sterile culture), 35 per cent had chronic pyelitis, and 16 per cent had bacteriuria only. Of 40 patients with puerperal pyelitis, 60 per cent were cured, 10 per cent had chronic pyelitis, and 30 per cent bacteriuria only. She concluded the outlook was better in puerperal pyelitis than in antenatal pyelitis. No patient in the series of antenatal cases suffered from an acute pyelitis in a subsequent pregnancy.

Traut and Kuder quote Hazelhorst, who studied 62 women, finding minor difficulties in 39, exacerbations in 19, and hypertension in 3. Also, Robecchi found in patients, five to thirty months after pyelitis, that 23 per cent were normal while 77 per cent showed some degree of hydroureter, albuminuria, pyuria, and bacteriuria.

In our study there are 28 patients who had pyelitis of pregnancy from five months to fourteen years ago. Twenty-one were antenatal

In only two patients were apparently normal pyelograms found. One of these has pain and tenderness in the right flank after five months, while the other has no complaints. Fifteen of these patients (53 per cent) at the present time have either backache, pain in the side or persistent pyuria, while the remainder have no complaints, but have not had complete studies.

In contrast to the literature our 7 cases of puerperal pyelitis show changes similar to the whole group. Six patients had hydronephrosis on the right, one marked, 2 moderate, and 3 slight. There were 4 with hydronephrosis on the left, 1 moderate, and 3 slight. Four had hydroureters on the right and 2 on the left. One contained a small stone and 1 pyeloureterogram was normal.

While the above findings are most numerous and appear very serious, the majority of these patients are by no means seriously ill. In some without symptoms and good drainage, we doubt that cystoscopic treatment after thorough investigation is necessary. In these the fibrosis may have been simply enough to destroy elasticity necessary for the return to normal after delivery, but not interfering with drainage. On the other hand, it would seem that in many cystoscopic treatments should have been instituted to eradicate infection and stasis. The general custom has been to dismiss patients after the fever of pyelitis has subsided, hoping that urinary antiseptics and time will result in cure. It is obvious that all patients with pyelitis during pregnancy and the puerperium should be followed by intravenous pyelograms, urine examinations, and bladder cultures as indications for further urologic treatment.

#### SUMMARY

1. Some degree of dilatation of the ureters and kidney pelves occurs in almost every case of normal pregnancy. This usually regresses to normal in from one to seven weeks after delivery, although apparently it may last much longer in certain cases.

2. Twenty-eight patients who had pyelitis of pregnancy from five months to fourteen years ago have been studied with intravenous or retrograde pyelograms. Twenty-six (93 per cent) showed some degree of abnormality in the x-rays, the more serious changes occurring in 18 (64 per cent).

3. The most frequent findings were hydronephrosis (71 per cent) and hydroureter (53 per cent) on the right side. Stones were present in two cases.

4. This large percentage of abnormalities indicates the necessity of careful urologic studies after pyelitis of pregnancy.

We wish to acknowledge the valuable work of Dr. J. D. Gordinier, who assisted in the preparation of this paper.

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TABLE II—CONT'D

CASE	AGE	GRAV- IDA	PYELITIS OF		SIDE	FOLLOW-UP SYMPTOMS	TIME SINCE DELIVERY	FOLLOW-UP PYELOGRAM
			PREG.	PUER- PER.				
22	30	iii	++++ 2 & 3		Bil.	Pains rt. side—pus		Hydronephrosis, rt., marked Hydronephrosis, lt., sl. Hydroureter, rt., mod.
23	32	iii	+++ 3rd	-- 2nd	Lt.	Pain lt. side persist. pus	3 yr.	Hydronephrosis, rt., mod., fuzzy Hydroureter, bil., mod.
24	20	i	+++	++	Rt.	Persistent pyuria	6 mo.	Hydronephrosis, rt., mod. Hydroureter, lt., sl.
25	24	i	++++		Bil.	Pain rt. side Occ. cystitis	1 yr. 5 mo.	Hydronephrosis, rt., sl. Hydroureter, rt. sl.
26	26	i		++++	Bil.	None	1 yr.	Hydronephrosis, bilat., sl.
27	30	ii	++++ 1st		Bil.	Pain lt. side	12 yr.	Hydronephrosis, rt., mod. Hydronephrosis, lt., sl. Hydroureter, rt., mod. Hydroureter, lt., sl.
28	38	i	++++		Rt.	Frequent cystitis	14 yr.	Tortuosity rt. ureter

and 7 post partum. All but one were of moderate or severe degree. Fourteen were primiparas and 14 multiparas. In 17, the right kidney was apparently solely or mainly involved, 8 were bilateral, and 3 were on the left side.

No records of urinary studies are available on any of the patients before the pyelitis of pregnancy occurred, and we have very few pyelograms made during the pregnancy involved. However, these patients were returned after a considerable period of time as shown in Table II. Intravenous pyelograms were made in 22 cases and retrograde pyelograms in 6 cases.

The abnormal findings were very numerous. Hydronephrosis was present on the right in 20 patients (71 per cent), marked in 5, moderate in 10, and slight in 5. Hydronephrosis was found on the left in 10 patients (35 per cent), marked in 1, moderate in 2, and slight in 7. Hydroureter was present on the right in 15 patients (53 per cent), marked in 1, moderate in 10, and slight in 4. Hydroureter on the left was found in 10 patients (35 per cent), marked in 1, moderate in 6, and slight in 3.

It is of interest that in 3 cases of hydronephrosis on the right side, the ureter arose high on the pelvis such as has been described in cases with an aberrant vessel. If due to a vessel this would apparently be a congenital abnormality, but it is interesting to speculate on the relation of the hydronephrosis of pregnancy to the persistence seen with the aberrant vessel.

Definite tortuosity of the ureter was prominent in 13 patients, on the right side in 9, and on the left in 5.

One patient showed such poor excretion of dye that only a portion of a tortuous left ureter could be seen. In the remainder the excretion was prompt and satisfactory pictures were obtained. This would probably indicate that kidney function in general was not greatly impaired.

In two patients there were stones in the left kidney. Both were found three years after delivery. One had a small asymptomatic stone in the upper calyx, while the other showed multiple large stones recently removed at operation.

These patients should not be dismissed by the obstetrician as soon as the temperature becomes normal and the condition regresses, but they should first have the benefit of the new treatment for pyelitis, that is sulfanilamide, mandelic acid, or sulfapyridine, the latter particularly for staphylococcus infections. If this were done for six weeks, during the time the ureter is trying to return to normal, possibly such results as we have found would not again occur.

## IS THERE A CLINICAL RELATIONSHIP BETWEEN PYELITIS OF PREGNANCY AND PRE-ECLAMPTIC TOXEMIA?\*

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**I**NTEREST in the possible relationship between pyelitis and the toxemias of pregnancy has been given renewed impetus by the work of Peters and his co-workers,<sup>10-12</sup> and others, on the role of pyelitis in the production of the toxemias of pregnancy.

Peters called attention to the fact that no convincing evidence of the causative factors of toxemias has been demonstrated and asserted that the syndrome designated toxemia has been wrongly named. He stated that toxemia, apart from pyelitis, should not be considered an entity. Calling attention to the prevalence of ureteral dilatation among pregnant women, he indicated that this condition is common among patients with toxemia, some of whom had not had a history of renal infection or other infection at the time the toxic symptoms began. Peters admitted that "hypertension usually appears only after pyelonephritis has persisted for a long time and has destroyed a large part of both kidneys." He stated also that women who have pyelitis when pregnant seldom escape irreparable and enduring damage if the pregnancy is allowed to proceed. Reviewing 320 cases of toxemia of pregnancy, Peters and his co-workers noted that 41, or 13 per cent, of the patients suffered at one time or another from pyelitis or pyelonephritis. Among 93 patients with pyelitis complicating pregnancy, these authors noted that 25 had hypertension or edema or both before pregnancy was terminated.

After studying 100 cases of pyelonephritis in nonpregnant individuals subjected to neuropsy Weiss and Parker, Jr.<sup>16</sup> concluded that chronic pyelonephritis results in the gradual diminution of kidney structure, "contracted kidney," and in decreased function; that patients who had pyelonephritis in early childhood showed a marked tendency for a certain type of toxemia of pregnancy to develop. Weiss estimated that pyelonephritis is responsible for 15 to 20 per cent of the total number of cases of malignant hypertension. In contrast to these findings, Acosta-Sison reported evidence of pyelonephritis in only one among 38 cases in which death from eclampsia was followed by neuropsy.

Hayes reported 20 cases in which pre-eclamptic toxemia was cured by ureteral drainage employed to relieve back pressure on the kidneys, which he postulated as the cause of toxemia. La Vake, Talbot, Johnston, Johnson and Nicholas and others have stated that the acute toxemias are produced by toxic products from the placenta damaged by infection from foci. On the contrary, Theobald observed the almost complete absence of eclampsia in Siam, where infection of the urinary tract is prevalent. Baird noted that patients with marked ureteral stasis with or without urinary infection have a normal or low blood pressure and are not subject to "albuminuria of pregnancy." He found that pyelitis seldom develops in women in whom albuminuria and a rise in blood pressure develop

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### DISCUSSION

DR. ROBERT A. ROSS, DURHAM, N. C.—This study re-emphasizes the necessity for a careful and prolonged follow-up of the urinary tract after infections and operative procedures which may leave a scar on this system which may later be translated in terms of frequency of urination, infection, obstruction, stone formation, and arterial kidney damage.

When one considers the anatomy of the ureter and its similarity to other smooth muscle of the gastrointestinal and genitourinary tracts, and when one recalls the proved effect of the sex sterols and pituitary substance on such muscle, it is perfectly orderly to ascribe a great many alterations to these factors. Occasionally we find the effect to be of benefit, as in the patient with stricture who became pregnant.

We have been interested particularly in the study of urinary infection in relationship to the toxemias of pregnancy, because the toxemia of pregnancy is our major obstetric complication. Our findings are in accord with the abstracted material from Dr. Mussey's paper. Pyelitis and urinary infection occur most often in our private patient group, toxemia in our clinic group. Private patients constitute only one-fourth of the admissions on our obstetric service, yet 60 per cent of the patients admitted for pyelitis are in this group. Twenty-five per cent of all obstetric admissions have some degree of toxemia as a complication, and 5 per cent of these have convulsive eclampsia. Yet again the urinary infection is not predominantly in this group.

Our follow-up would lead us to agree with the authors' figures as to the time elapse before a return to normal, as would other observations of the post-partum woman. It is more likely to be six weeks or six months, rather than one to six weeks, before the female organism is again normal.

DR. FREDERICK H. FALLS, CHICAGO, ILL.—There are three points that I would like to make in connection with a discussion of these two last papers. The first is that physiologically there is a change in the lower end of the ureter during pregnancy. That change is a hypertrophy of the sheath of Waldeyer which tends to close or constrict, or form more of a sphincter at the lower end of the ureter than is normally present in the nonpregnant woman.

The second point is that the uterus and the urinary tract arise from the same embryologic *anlage*, and to me it is quite impossible to conceive of a mechanism that has been provided to prevent the uterus from emptying itself, without it affecting the mechanism for the extrusion of urine. It has been observed that in pregnant women, especially those with pyelitis, the urinary peristalsis, as estimated by watching the extrusion of dye from the urinary meatus by cystoscopic examination, is much slower on the normal side as compared with the normal patient, and on the affected side as compared with the normal side of the affected woman. Now the normal mechanism for the retention of the fetus in the uterus is hormone, and progesterone is an antipituitrin. This peculiar recovery that occurs must, it seems to me, be due at least in part to the action of progesterone on the ureter, helping possibly by stasis to prevent increasing the likelihood of infection ascending from the bladder and producing pyelitis.

Another reference I would like to make is to the pathology that is present in the ureters of women who have had pyelitis. It was my misfortune to have a patient die of post-partum hemorrhage which was due to a severe anemia produced by the pyelitis. Anemia associated with pyelitis has not been sufficiently appreciated. A study of the urinary tract will show us why Dr. McConnell finds these changes persisting over some months. Probably the ureter never returns to normal after having suffered a serious pyelitis change.

DR. GRAY (closing).—It seems likely that progesterone will be the hormone found to cause dilatation of the ureter. It is now possible to obtain progesterone in large doses and certainly such a hormone should be studied on normal dogs or other animals.

In order to determine the possible clinical relationship between pyelitis of pregnancy and pre-eclamptic toxemia, the case histories of pregnancies complicated by either one or both of these diseases have been scrutinized. The case histories of patients with pyelitis of pregnancy and of the puerperium have been examined to ascertain whether acute toxemia developed (1) during the course of pregnancies complicated by pyelitis or (2) in subsequent pregnancies occurring under our supervision. The case histories of all certain cases of acute late toxemia of pregnancy were examined to determine (1) how many of these patients had pyelitis antecedent to pregnancy and (2) in how many evidence of pyelitis developed during the puerperium.

This review embraced the study of histories of 117 proved cases of pyelitis complicating pregnancy and 163 cases of acute hypertensive toxemia of late pregnancy seen at the Mayo Clinic between Jan. 1, 1924, and Dec. 31, 1937, inclusive. Only cases of pre-eclampsia and eclampsia are included in the toxemic group and in each case the history or examination must have furnished sufficient data to determine the presence or absence of complicating pyelitis. The number of cases in the acute hypertensive group is relatively small because cases of doubtful diagnosis or those with evidence of antecedent vascular or nephritic disease, except possible pyelitis or pyelonephritis, were discarded. The diagnosis of all cases of pyelitis is based on the presence of pus and often red cells in catheterized urine, fever, usually chills and often symptoms such as pain along the urinary tract, urinary disturbance and physical findings of costovertebral and abdominal tenderness. In practically all cases observed during the later years of this review the infecting organism was determined by culture of the urine. Among those patients observed early in this series a large majority were examined cystoscopically, and in 42, or 36 per cent, of the entire series the diagnosis was confirmed in this manner.

Among the 117 patients with pyelitis, in 92 the disease occurred in the course of pregnancy and in 25 in the puerperium. In the case of 3 patients, pyelitis of pregnancy was followed or accompanied by the development of acute toxemia. A fourth patient (Case 4) with fulminating pyelonephritis died with acute renal failure probably associated with cortical abscesses; necropsy was not obtained, and it is debatable whether this case should be classed as a true pre-eclamptic toxemia.

#### REPORT OF CASES OF PYELITIS OF PREGNANCY THAT PRECEDED THE APPEARANCE OF PRE-ECLAMPTIC TOXEMIA

CASE 1.—The patient had severe bilateral pyelonephritis at three and one-half months after the beginning of her first pregnancy. Pre-eclamptic toxemia developed during the eighth month and she still had pus Graded 4, on a basis of 1 to 4, in the urine. She had four subsequent pregnancies and even though she showed evidence of a mild degree of chronic nephritis there was no flare-up of acute toxemia or pyelitis. This is the only case in this series in which evidence was obtained of residual kidney damage with lowered renal function following pyelitis of pregnancy.

during pregnancy and in the very few cases in which urinary infection has been observed it has been transitory. Baird stated that these patients are more susceptible to pyelitis of the puerperium. Herrick agreed that pyelitis of pregnancy is a fairly common complication, but usually exists apart from any manifestations of so-called toxemia, and McLane stated that there is no proved relationship between pyelitis and the toxemias of pregnancy.

The writings of various observers indicate a difference of opinion concerning the incidence of pyelitis. Baird reported that 20 per cent of the women admitted to the antenatal wards of a London hospital during their first pregnancy had pyelitis; these patients comprised more than one-third of all patients admitted with pyelitis of pregnancy. In contrast to this high incidence are the low percentages reported by other authors: Traut, 2 per cent; Crabtree 2.5 per cent among 4,662 deliveries; Cabot, quoting members of the Boston Obstetrical Society, 0.7 per cent; and recently, McLane, 1.2 per cent among 14,000 deliveries. One hundred and seventeen patients with a positive diagnosis of pyelitis of pregnancy were observed at the Mayo Clinic during the years 1924 to 1937, inclusive; during this period there were 5,960 deliveries, an incidence of pyelitis of practically 2 per cent. This ratio of approximately two cases of pyelitis among one hundred pregnant women is similar to that of most of the reports previously cited. This review indicates also that pyelitis occurs more frequently in the first than in subsequent pregnancies.

At the outset of this discussion of the possible relationship between pyelitis of pregnancy and pre-eclamptic toxemia, it should be made clear that we are using the generally accepted term, toxemia, as a part of the name for the acute hypertensive syndrome of late pregnancy commonly called pre-eclamptic toxemia; by its use we do not intend to affirm or deny hypotheses that the syndrome of pre-eclamptic and eclamptic toxemia is necessarily due to a toxin or toxins.

There remains considerable confusion concerning an acceptable classification of the toxemias of pregnancy. In order to clarify our use in this paper of the terms, pre-eclampsia and eclampsia, we are including the following classification of the toxemias of pregnancy agreed upon by a subcommittee of *The American Committee on Maternal Welfare*: vomiting of pregnancy, pre-eclampsia, eclampsia, renal disease, hypertensive disease, and an unclassified group. Possibly acute yellow atrophy of the liver should be included; this and vomiting of pregnancy may be disregarded in this discussion. The acute hypertensive toxemias of late pregnancy (the third trimester) are pre-eclampsia and eclampsia, whose entire syndrome has developed in the course of a given pregnancy; in this respect the acute toxemias are distinct from cardiovascular-renal conditions with which the woman was affected prior to pregnancy and which are prone to exhibit symptoms of exacerbation earlier in pregnancy than the third trimester. Complete discussion of the unclassified group is not pertinent to this paper. In it are placed cases whose symptoms and findings do not permit of definite diagnosis and classification; for example, sometimes it is impossible to differentiate between acute pre-eclamptic toxemia and certain cases of mild antecedent vascular disease with superimposed toxemia.

The terms ureteritis, pyelitis, and pyelonephritis need no explanation. Since it is frequently impractical or impossible to determine during pregnancy the extent of involvement of the urinary tract in cases of acute infection, the term, pyelitis, is used in this paper to indicate inflammation of any or all portions of the upper urinary tract.



CASE 14.—The patient had previous acute pyelonephritis and left ureterolithotomy. She had repeated attacks of pyelitis during her fourth pregnancy but revealed no signs of toxemia.

None of the 163 patients with pre-eclamptic toxemia gave a history of pyelitis prior to the first pregnancy; in 6 cases pyelitis developed during the puerperium.

#### REPORT OF CASES OF ACUTE TOXEMIA IN WHICH PYELITIS LATER DEVELOPED

CASE 15.—The patient was referred to us with eclampsia. Symptoms of pyelitis developed on the third day of the puerperium.

CASE 16.—The patient suffered from rather severe pre-eclamptic toxemia during her first pregnancy. Two days post partum she had the onset of pyelitis.

CASE 17.—The patient had a mild toxemia with her first pregnancy and pyelitis developed three days post partum.

CASE 18.—The patient had mild toxemia with her first pregnancy and pyelitis developed two days post partum.

CASE 19.—The patient had post-partum pyelitis following her first pregnancy in which she had had pre-eclamptic toxemia.

CASE 20.—The patient had 5 normal pregnancies. During the sixth pregnancy she had pre-eclamptic toxemia. Two months after her eighth child was born she had an attack of acute cystitis and pyelitis. She had 2 subsequent normal pregnancies.

#### COMMENT

The publications of Peters and his co-workers and others on pyelitis and pyelonephritis have given renewed impetus to the interest among obstetricians in the possible relationship between pyelitis and the toxemias of pregnancy. Pyelitis may be of sufficient severity and duration to damage the kidney structure and curtail renal function. Pregnant women with lowered renal function caused by severe pyelitis are subjected to increased hazard as well as are those with lowered function resulting from other renal diseases or from generalized vascular disease. Hypertension is the predominant finding in the acute toxemias of late pregnancy; it is rarely present in cases of acute pyelitis or pyelonephritis. Acute systemic arteriolar changes of a spastic nature have been reported by many observers among many cases of pre-eclamptic toxemia and eclampsia, but rarely have such changes been found in cases of acute pyelitis. Our clinical data indicate that acute pyelitis of pregnancy is rarely either the indirect or direct cause of acute hypertensive toxemias which arise in the course of pregnancy.

Among 117 cases of pyelitis of pregnancy, acute hypertensive toxemia developed in three and a fatal inflammatory kidney lesion developed in a fourth. Among 163 patients with pre-eclamptic toxemia or eclampsia, 6 showed symptoms of pyelitis in the puerperium; none gave a history of pyelitis prior to the first pregnancy. The 2 per cent incidence of pyelitis among this group of pregnant women appears to correspond with the findings of the majority of other observers. When treatment was instituted early a large majority of these cases of pyelitis responded with reasonable promptness to the usual medical methods of treatment so that in recent years the necessity for urologic consultation has been infrequent.

CASE 2.—The patient had an attack of pyelitis during the fourth month of her first pregnancy. She carried to term and delivered a normal baby. In the course of her fifth pregnancy, pre-eclamptic toxemia developed.

CASE 3.—The patient had 2 normal pregnancies. During the fourth month of her third pregnancy she had a severe attack of pyelitis which responded to treatment. She had 5 subsequent normal pregnancies; during the ninth pregnancy she had a severe grade of acute toxemia which necessitated interrupting the pregnancy.

CASE 4.—The patient had an attack of bilateral pyelitis in the eighth month of her first pregnancy and was extremely ill with high temperature when referred to us ten days later. The disease did not respond to treatment, including the use of indwelling ureteral catheters. Following spontaneous onset of labor she delivered on the fourth day after admission. After a septic course she died on the twelfth day post partum from renal insufficiency (nonprotein nitrogen 171), probably with renal cortical abscesses; necropsy was not obtained.

Thirty women who had pyelitis of pregnancy were under our care during one or more subsequent pregnancies without showing evidence of recurring pyelitis; in 2 cases (Cases 2 and 3) noted in the preceding paragraphs, evidence of toxemia developed in a subsequent pregnancy. It is of interest that acute toxemia did not develop among 10 patients, each of whom had an attack of pyelitis either prior to or in the course of pregnancy and one or more subsequent attacks of pyelitis in the course of ensuing pregnancies.

#### REPORT OF CASES WITH HISTORY OF TWO OR MORE ATTACKS OF PYELITIS IN WHICH TOXEMIA DID NOT DEVELOP

CASE 5.—The patient had had recurring attacks of pyelitis for three years previous to her first pregnancy. She had an attack during this pregnancy but no signs of toxemia.

CASE 6.—The patient had an attack of pyelitis two years prior to her first pregnancy and an attack during the sixth month of gestation. She showed no signs of toxemia during this pregnancy nor in one subsequent pregnancy of which we have record.

CASE 7.—The patient had pyelitis prior to her second pregnancy and an attack of pyelitis during this pregnancy. She had 3 subsequent pregnancies without toxemia.

CASE 8.—The patient had pyelitis prior to her second pregnancy, and during the sixth month of this pregnancy. She had two subsequent pregnancies without toxemia even though signs and symptoms of pyelonephritis persisted after delivery of her fourth baby.

CASE 9.—The patient had pyelitis previous to her second pregnancy and an attack during the sixth month. She had one subsequent pregnancy without toxemia.

CASE 10.—The patient had an attack of pyelitis with her first pregnancy and an attack during the eighth month of her second pregnancy. She had 2 subsequent pregnancies without toxemia.

CASE 11.—The patient had pyelitis five years prior to her first pregnancy, and an attack during the sixth month of this pregnancy. There were no signs of toxemia.

CASE 12.—The patient had an attack of pyelitis with her first pregnancy and during the last month of her second pregnancy; there were no signs of toxemia.

CASE 13.—The patient had a left nephrectomy prior to her first pregnancy. An attack of right pyelitis developed during the sixth month of gestation but there were no signs of toxemia.

are toxic to the mother and in degrees varying with degrees of toxicity of the products of conception. If the products of conception are not toxic to the mother, no amount of infarction will cause true late toxemia, although progressive absorption of the dead products may give signs in the mother such as would occur if she were absorbing her own dead tissue. To my mind, pyelitis may be a direct cause of toxemia by infarction of the placenta and an indirect cause by lowering excretory efficiency.

DR. H. W. JOHNSON, HOUSTON, TEXAS.—It may be that further study will enable us to divide our cases of pyelitis into subgroups, and the men in the north may see the kind that we sometimes see in the south, namely, pyelitis accompanied by bleeding, especially from the uterus and cervix.

In four autopsies at our hospital, on deaths from eclampsia, occurring nine days after the convulsions, 3 were complicated by pyelonephritis and 1 by acute miliary tuberculosis. It was hard to say in those cases how much could be attributed to the pyelonephritis or to the tuberculosis.

DR. MUSSEY (closing).—It would be a very interesting thing if others would review their clinical records of patients who have had pyelitis of pregnancy and those with toxemia, and perhaps develop a combined report.

I wondered whether the bleeding Dr. Johnson spoke of might not be due to streptococic pyelitis. We have noticed that where there had been a streptococic infection in association with pyelitis there has been a little tendency to bleed.

Another point which has become evident to us and to the urologists associated with our group is that the urologist is not called in consultation on these cases of pyelitis as often as he used to be. Some ten or more years ago the urologist was called in consultation immediately, and it was taken for granted that the accepted treatment was ureteral catheterization. Gradually it has become evident that if the disease is diagnosed early and treated promptly, ureteral catheterization is rarely necessary.

It has been said that any woman who has had vascular or renal disease, including pyelitis, should not be allowed to proceed with pregnancy. This statement is too inclusive as patients with such conditions should be individualized. Women with undoubted renal disease should be advised against subsequent pregnancy. Some recover from acute renal disease and in others the residual damage is so mild as to escape the usual methods of examination. Among this group of patients with pyelitis, 30 were carried through one or more subsequent pregnancies; in 2 cases of the 4 previously mentioned, toxemia developed in a subsequent pregnancy.

The results among the cases here reported would indicate that acute pyelitis of pregnancy when treated promptly is not prone to cause pre-eclamptic toxemia or eclampsia, and that following one attack of acute pyelitis of pregnancy the majority of such women do not exhibit symptoms of residual renal damage.

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#### DISCUSSION

DR. R. T. LAVAKE, MINNEAPOLIS, MINN.—I have made a study of the urinary findings of all pyelitis and late toxemia cases, occurring on the Obstetric Service at the Minneapolis General Hospital during the past ten years. In a total of 15,740 admissions (14,653 deliveries), there were 63 diagnoses of pyelitis unassociated with late toxemia. There were 373 cases of late toxemia. According to the criteria for diagnosis used by Dr. Mussey, the incidence of pyelitis in these toxemic patients was 3.22 per cent. By the most stringent standard of normality for urinary findings set by the laboratory, according to their technique, 72.85 per cent were absolutely normal. This left a group containing 23.93 per cent of the cases of toxemia in which, upon urinary findings alone, one might diagnose varying degrees of urinary infection. There was no correlation between the presence, intensity, or absence of urinary infection, and the presence, intensity, or absence of toxemia.

Time, and the elusive character of general hospital material, made it impossible to determine how many of the cases of pyelitis, unassociated with toxemia during their hospitalization, later developed toxemia. Dr. Mussey's material shows a percentage of 3.26 per cent. This is a most important figure because it gives us an approximate figure of the limits within which pyelitis is likely to operate as a mechanism, if our belief is correct that it can so operate.

Laying aside figures and entering the realm of the theory founded upon personal clinical observation and research, I would expect pyelitis to be but an infrequent mechanism in the causation of toxemia. In the first place, infection is only one possible cause of infarction, and clinical findings suggest that it does not always infarct the placenta; and, in the second place, when it does lead to infarction, it is my belief that toxemia will manifest itself only if the products of conception

*Gynecogen*: A collective term for all substances which are able to restore, to some extent, the female genital tract following castration atrophy, or stimulate its growth directly; or induce or maintain, or both, the secondary sex characteristics of the female.

This group is subdivided into two groups of substances: *estrogens* and *progestogens*.

*Estrogen*: "A collective term for all substances producing an estrous (proliferative) growth in vagina, uterus, and mammary glands and female secondary sex characteristics."<sup>7\*</sup>

*Progestogen*: A collective term for all substances which have the property of producing progestational changes in the female genital tract. (It has become necessary to introduce this term since it has been found that *progesterone*, the pure hormone of the corpus luteum, is not specific in this respect. The term *progestin* refers to impure extracts of the corpus luteum containing a substance having the properties of progesterone.)

Significant, too, are the bisexual potentialities of the gonad, especially in the female, both on an embryologic and biologic basis;<sup>2, 3</sup> thus it is not surprising to learn that normal ovaries implanted in castrate males may maintain their secondary sexual organs.<sup>4</sup> Moreover, it has been demonstrated that normal human females may excrete as much androgenic substance in their urine as do normal men.<sup>5</sup> On the other hand, bull's testes (per weight) and stallion's urine (per volume) are among the richest known sources of estrogenic substances.<sup>6</sup>

The bisexual nature of the sexual hormones is well exemplified by testosterone. In Table I is presented a short outline summary of some of these properties of testosterone compared with those of estrone and progesterone. Study of the data offered reveals that the gynecogenic activity of testosterone is dual, for it may act like an estrogen or a progestogen.

The concept of neutralization of estrogens by testosterone cannot be accepted as a mathematical plus-minus equation. The evidence presented in Table I clearly demonstrates that, in the main, estrone, and testosterone exert a cooperative synergistic action on the female genital tract when given in physiologic amounts. Rather than neutralize, testosterone merely modifies the actions of estrogens. In this respect testosterone may act like progesterone. This would result in an increased excretion of estrogens, as well as cause a shift in the estradiol-estrone-estriol equilibrium to the right.<sup>63, 64</sup> An increased excretion of estrogens following the administration of testosterone has been observed.<sup>65, 66</sup>

In short, after surveying the evidence, one may as rightfully call testosterone a "female" sex hormone as a "male" sex hormone.

## II. THE MYOMETRIAL ELEMENTS PLAY AN ESSENTIAL ROLE IN CONTROLLING THE VOLUME OF BLOOD FLOWING TO THE ENDOMETRIUM, AND THUS, THE AMOUNT OF UTERINE BLEEDING. THE TWOFOLD ACTION OF TESTOSTERONE UPON THESE MYOMETRIAL ELEMENTS IS SUCH THAT EXCESSIVE UTERINE BLEEDING IS CONTROLLED

The mode of action by which testosterone propionate is able to check uterine bleeding will not be explained fully until it is first known what

\*Allen, E.: Sex and Internal Secretions, ed. 2, Baltimore, 1939, Williams and Wilkins Co., p. 453.

# RATIONALE FOR THE USE OF TESTOSTERONE PROPIONATE IN THE IMMEDIATE TREATMENT OF EXCESSIVE UTERINE BLEEDING\*

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## INTRODUCTION

EXCESSIVE uterine bleeding, next to dysmenorrhea, is the most common disorder of menstruation. Therapeutic trials for relief, with chorionic gonadotropin (pregnancy urine extracts), corpus luteum extracts, and progesterone revealed that their effectiveness was limited.<sup>1</sup> In the search for a more potent agent, investigators have recently presented what promises to be a very effective weapon in controlling excessive uterine bleeding. This substance is the so-called "male" sex hormone, testosterone, most commonly used as its propionic acid ester, testosterone propionate. This report presents a consideration of certain properties of this hormone, noting especially its dual gynecogenic properties. In particular, the two-fold action of testosterone upon the myometrial elements is correlated with certain anatomic and physiologic evidence concerning the uterine circulation at the time of menstruation. On this basis, a reasonably clear working hypothesis has been developed along physiodynamic lines to explain the *modus operandi* by which testosterone may control excessive uterine bleeding. Clinical studies on parenteral and oral therapy, and subcutaneous implantation of pellets of testosterone propionate are discussed.

## I. TESTOSTERONE IS NOT ONLY A POWERFUL ANDROGEN BUT ALSO A VERY POTENT GYNECOGEN

One of the most important contributions to our knowledge of sexual physiology has been the recognition of the fact that all of the sexual hormones possess bisexual properties. Each possesses, to a different extent, both androgenic and gynecogenic activity.

For the purpose of both simplifying and clarifying nomenclature, the following scheme of terminology has been adopted:

All of the sexual hormones are definitely bisexual in their action. Where the action is exerted in the direction of "maleness," the term *androgenic* is used. Where the action is exerted in the direction of "femaleness," the term *gynecogenic* is used.

*Androgen*: A collective term for all substances which are able to restore, to some extent, the male genital tract following castration atrophy, or stimulate its growth directly; or induce or maintain, or both, the secondary sex characteristics of the male.

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The clinical studies were carried out in the Departments of Gynecology of the Johns Hopkins Hospital and the Sinai Hospital, Baltimore, Maryland.

The experimental studies were performed in the laboratories of Dr. Carl G. Hartman at the Carnegie Institute of Anatomy and Embryology, Baltimore, Maryland.

TABLE I. COMPARISON OF SOME EFFECTS OF TESTOSTERONE WITH THOSE OF ESTRONE AND PROGESTERONE, ILLUSTRATING SOME OF THEIR BISEXUAL PROPERTIES AS WELL AS THE DUAL GYNECOGENIC PROPERTIES OF TESTOSTERONE

	RESPONSE TO PROGESTERONE	RESPONSE TO TESTOSTERONE	RESPONSE TO ESTRONE
<i>(Castrate not primed with estrogen)</i>			
Uterus Endometrium	Proliferative and progestational <sup>7</sup>  Monkey, rabbit, rat	I. Proliferative <sup>8, 9</sup> Monkey, guinea pig  II. Proliferative and progesta- tional <sup>10-12</sup> Cat, rat, rabbit	Proliferative <sup>13</sup> Human being, mon- key, et alia
Myometrium Growth	Slight <sup>7, 14</sup> Monkey, rat, rabbit	Marked <sup>10, 11</sup> Rat, cat, rabbit	Marked <sup>10, 13</sup> Human being, mon- key, et alia
Rhythmic motility	None <sup>15</sup> Rabbit		Induced <sup>15</sup> Human being, mon- key, et alia
Tubal motility			Induced <sup>15, 16</sup> Human being, rabbit
Vagina	Slight proliferation and mucifica- tion <sup>7, 13</sup>  Rat	Marked growth, proliferation and incomplete muci- fication <sup>10</sup>  Rat	I. Marked growth, proliferation, strati- fication and cornifi- cation <sup>10, 13</sup> Human being, mon- key, rat, et alia II. Mucification (sub- threshold doses) <sup>17</sup> Rat
Breast	Apparently none <sup>18</sup>  Rat	Slight duct prolifer- ation and lobular growth <sup>18, 19</sup>  Rat	Duct prolifera- tion <sup>18, 19</sup>  Rat, human being, monkey, et alia
<i>(Castrate primed with estrogen)</i>			
Uterus Endometrium	I. Proliferative and progesta- tional <sup>7, 13</sup> Human being, monkey, et alia II. Hypoplasia (chronic experi- ments) <sup>7, 20</sup> Monkey, rabbit	I. Proliferative and progesta- tional <sup>10-12, 22</sup> Cat, rat, rabbit  II. Hypoplasia (chronic experi- ments) <sup>23, 24</sup> Monkey, rabbit III. Prolifera- tive <sup>8, 21</sup> Monkey	I. Proliferative <sup>13</sup>  Human being, mon- key, et alia II. Hypoplasia (chronic experi- ments) <sup>25, 26</sup> Monkey, rabbit
Myometrium Growth	Moderate <sup>7, 14</sup> Monkey, rabbit, et alia	Marked <sup>10-12</sup> Rat, cat, rabbit	
Rhythmic motility	Inhibition <sup>15</sup>  Human being, rab- bit, et alia	Inhibition <sup>22, 27, 28</sup>  Human being, rabbit	Inhibition (chronic experiments) <sup>26</sup> Rabbit

factors initiate, what forces maintain, and what combination of circumstances stop the menstrual flow. However, there have recently appeared several excellent anatomic investigations on the menstruating human<sup>67</sup> and monkey<sup>68, 69</sup> uteri. Based on these as well as certain studies on the effect of various sex hormones on the circulation in the uterus of the monkey, and, keeping in mind certain physiologic properties of testosterone, a reasonably clear working hypothesis has been developed on a physiodynamic basis.

Well established, indeed, is the fact that uterine bleeding (exclusive of neoplasms and pregnancy) may proceed from every known type of endometrium (proliferative, secretory, hyperplastic, atrophic, or inflammatory). The only common denominator to all of these is the recurrent vascular phenomena in the spiral arterioles. In brief, *menstruation is fundamentally a vascular phenomenon*.

The spiral arterioles arise from the arcuate branches of the uterine artery in the middle third of the myometrium, wind inward, become radial in their course through the inner fourth of the myometrium, and finally extend toward the endometrial surface. Most of them do not give off any branches in the endometrium. They are definitely under hormonal control, for, following castration, these vessels atrophy.<sup>69</sup> Throughout the menstrual cycle these vessels proliferate with the endometrium. Since they grow more rapidly than the uterine mucosa, they become more and more tortuous, until, premenstrually, they assume a more or less spiral shape, whence their name.<sup>68</sup> The vessels supplying the deep portion of the endometrium, the basalis, do not undergo cyclical changes.<sup>68, 69</sup>

Immediately preceding menstruation, these spiral arterioles alternately constrict and dilate, giving rise to the so-called blush and blanch phenomenon.<sup>70</sup> Then the peripheral portion of these arterioles dilates, one by one, in widely disseminated portions of the mucosa, and at varying intervals, extravasation of blood occurs, which, combined with retrograde flow from the venous capillary bed, appears externally as menstruation. This is soon followed by a marked reduction in the circulation to the area in the mucosa from which extravasation occurred, produced by vasoconstriction of the arteriole supplying that area.

Where does this functional vasoconstriction occur? From a study of the arterioles in the uterine mucous membrane at the time of menstruation, Bartelmez concludes that, because of the extremely great variability found in them, the explanation for the reduction or stoppage of the flow of blood to the mucosa must be sought for in the myometrium and not in the endometrium.<sup>67</sup>

Let us examine the evidence for such possibilities in the myometrium. The spiral arterioles possess an intimate relationship with the myometrial elements. In the monkey, as these vessels pass through the inner fourth of the myometrium, there are distinguishable closely about them bands of specialized muscle tissue, which Daron<sup>68</sup> has called "contraction cones." In the human being, Bucura<sup>71</sup> has described longitudinal groups of muscle fibers, or "Polster," immediately beneath the tunica intima of the arteries in the female genital tract. These Polster of



Bucura have been found especially abundant in the inner fourth of the myometrium and in the stratum vasculare. Keiffer has demonstrated that the fibers of the tunica media of these arteries are continuous with the intrinsic muscle fibers of the myometrium.<sup>72</sup> Further, Okkels and Engle<sup>69</sup> in the maeaque, and Keiffer<sup>72</sup> and Durante<sup>73</sup> in the human being, have described a peculiar sphincter-like arrangement of myometrial fibers about the large vessels in the stratum vasculare. Here bundles of muscle fibers, forming S-shaped loops, interweave with the tunica media of adjacent arteries and veins. In short, the intimate association between the blood vessels and the muscle fibers in the myometrium is such that adequate contraction of the muscular elements would very markedly diminish the flow of blood to the endometrium. The analogy to the bleeding post-partum atonic uterus, and the effects of oxytocics on it, is obvious.

Important, too, in connection with the vascular physiology of the uterus is its rhythmic intermittent contractility, initiated and maintained by estrogens. Immediately before and during menstruation there is a gradual rise in the estrogens in the blood and urine.<sup>74, 75</sup> This rise is much more likely to be pronounced in cases with functional uterine bleeding.<sup>6, 64, 74, 76</sup> The human uterus has been found to be actively contracting just before and during menstruation.<sup>77</sup> Intermittent rhythmic contractility serves to increase the volume flow of blood through the dilated endometrial vessels, because of the pumping action of the movements.<sup>78</sup> This increase follows the initial hyperemic effect of the estrogens.<sup>15</sup>

It now becomes clear that excessive uterine bleeding will occur if the proximal (myometrial) portion of the spiral arterioles fails to constrict, or be constricted, following the initial extravasation of blood distally. Therefore, regardless of the precipitating factor, be it myomas, subinvolution, pelvic inflammatory disease, or merely "functional," one of the basic causes for excessive uterine bleeding is a disruption of the normal hemodynamics of the uterine circulation at the time of menstruation, aided and abetted by a disturbance in the normal pattern of uterine contractility at the same time.

Let us now turn our attention to the physiologic properties of testosterone propionate. From study of Table I, it is noted that the effect of this hormone upon the endometrium is variable. The status of the endometrium, however, is practically unimportant as regards uterine bleeding. In contrast, the response of the myometrial elements is clear-cut and far more significant. The effects of testosterone are twofold. First, this hormone will inhibit the estrogen-induced rhythmic contractility of the uterus.<sup>22, 28</sup> As a result, the volume flow of blood to the uterus will be decidedly diminished,<sup>78</sup> for the activity of muscle and its blood supply are, within limits, directly proportional.<sup>79</sup>

In addition, testosterone exerts a direct stimulative action upon the myometrial elements.<sup>10</sup> Inhibition of intermittent uterine contractions is not accompanied by a true relaxation, but merely by a decrease in tension.<sup>30</sup> Grossly, the uteri of rabbits and rats, especially after chronic injections of testosterone propionate, appear shrunken.<sup>48, 80</sup> Biopsies

	RESPONSE TO PROGESTERONE	RESPONSE TO TESTOSTERONE	RESPONSE TO ESTRONE
Tubal motility	Inhibition <sup>15, 16, 29</sup>	Inhibition <sup>30, 31</sup>	Inhibition (chronic experiments) <sup>30, 32</sup>
	Human being, rab- bit	Rabbit, human be- ing	Human being
Vagina	Mucification <sup>7, 10, 13</sup>	Marked growth and mucification <sup>10</sup>	
	Rat, mouse	Rat	
Breast	Lobulation <sup>18</sup>	Incomplete lobula- tion <sup>18</sup>	
	Monkey, rabbit, et alia	Rat	
Ovulation	I. Inhibition <sup>33</sup>	I. Inhibition <sup>23, 35</sup>	I. Inhibition <sup>37</sup>
	Rat, rabbit	Human being, mon- key, et alia	Monkey, rat, et alia
	II. Stimulation <sup>34</sup>	II. Stimulation <sup>34, 36</sup>	II. Stimulation <sup>38</sup>
	Toad	Rat, mouse, toad	Rat
Menstruation	Inhibition <sup>7, 39</sup>	Inhibition <sup>23, 24</sup>	Inhibition <sup>40, 41</sup>
	Monkey	Human being, monkey	Human being, monkey
Pregnancy			
Ovaries intact	Prolonged <sup>42</sup>	Prolonged <sup>43</sup>	Prolonged <sup>44</sup>
Ovaries removed	Rabbit	Rat	Rabbit
	Maintained <sup>45</sup>	Maintained <sup>46</sup>	Not maintained <sup>45</sup>
	Rabbit	Rat	Rabbit, rat
Lactation	No inhibition <sup>47</sup>	I. Partial inhibi- tion <sup>47</sup>	I. Inhibition <sup>47</sup>
	Rat	Rat	Human being (?), rat, et alia
		II. No inhibition if baby continues to nurse <sup>27</sup>	II. No inhibition if baby continues to nurse <sup>48</sup>
		Human being	Human being
Gonadotropic factor (Ant. pituitary)	Depressed <sup>33, 49</sup>	Depressed <sup>50, 51</sup>	Depressed <sup>37, 51</sup>
	Rabbit, human be- ing	Rat, human being, et alia	Rat, human being, et alia
Corpus luteum (life of)	Apparently pro- longed <sup>52</sup>	Prolonged <sup>52, 53</sup>	Maintained and pro- longed <sup>54, 55</sup>
	Rat	Rat	Rat, rabbit
Vagina (imma- ture rat)	Slight <sup>7</sup>	Premature opening and slight mucosal proliferation <sup>56</sup>	Premature opening and proliferation of mucosa <sup>13</sup>
Spermatogene- sis (hypoply- scetomized rats)	Maintained <sup>57</sup>	Maintained <sup>57</sup>	
Prostate (castrate)	Restoration of mucosa toward normal <sup>58, 59</sup>	Restoration of mu- cosa to normal <sup>59</sup>	Growth and squamous metaplasia <sup>59</sup>
	Rat	Monkey, dog, rat	Dog, rat, et alia
Testicular descent		Stimulation <sup>48, 60</sup>	Inhibition <sup>61</sup>
		Human being, monkey, et alia	Rat
Penis (imma- ture)	Hastened growth <sup>48</sup>	Hastened growth <sup>60, 62</sup>	Partial inhibition <sup>62</sup>
	Rat	Human being, monkey, et alia	Rat, mouse

(Only key references are given.)

of these uteri in the intact treated animal are practically bloodless, whereas those from normal untreated animals bleed freely.<sup>48, 50</sup> Moreover, in the human being, the actively contracting puerperal uterus, experienced by the patient as "after-pains," can be quieted with testosterone propionate.<sup>27</sup> At first, the contractions can be felt to diminish in amplitude and somewhat in frequency. At the same time, the uterus can be felt to become firmer and firmer.

Further proof of the direct action of testosterone upon the myometrial elements is offered by the following experimental data. In Fig. 1 is seen a section through the uterus of a castrate monkey who, primed and then maintained with estradiol dipropionate, had been given 1 mg. of crystalline progesterone in oil daily for twenty days. The arterial system was then injected with India ink. The dark black areas represent the blood vessels in the uterus. It is evident on first glance that this organ is very vascular. The large dilated endometrial vessels are clearly outlined. Fig. 2 reveals the uterus of a castrate monkey, similarly primed and maintained, who had received 1 mg. of crystalline progesterone in oil daily for ten days and then 25 mg. of testosterone propionate in oil daily for ten days more. (This dosage was derived from the data of Klein and Parkes<sup>12</sup> who state that the progestational response in rabbits to testosterone propionate is about one-twentieth that of progesterone.) She, also, was injected with India ink. Study of Fig. 2 reveals that the stratum vasculare is not reduced in the density of its vascular population, but in the size of its vessels. It is clearly evident, however, that there has resulted a very marked diminution in the endometrial circulation.

Summing up the evidence, the following conclusions concerning the effect of testosterone upon the myometrial elements appear valid. The volume flow of blood *to* the uterus is definitely reduced by the inhibition of intermittent uterine contractions by testosterone. The volume flow of blood *in* the myometrium, especially in its inner fourth, is decidedly diminished by the direct stimulative action of testosterone upon the myometrial elements, bringing about a functional constriction of the myometrial vessels. The significance of the close anatomic interrelationship between the blood vessels and the muscle fibers of the myometrium now becomes manifest. (A possible added direct action upon the myometrial vessels themselves, however, is not excluded.) Clearly, then, the net result of the twofold action of testosterone upon the myometrial elements will be a marked reduction in the volume flow of blood *to* the endometrium. It follows, therefore, that there will occur a consequent decided decrease in the amount of uterine bleeding. Thus, on a physiodynamic basis, is presented a reasonably clear and logical rationale for the use of testosterone propionate in the immediate treatment of excessive uterine bleeding.

### III. CLINICAL STUDIES

Twenty-five patients with excessive uterine bleeding were treated. Their ages ranged from 15 to 49 years. Endometrial studies showed cystic hyperplasia 14 times, an interval non-secretory phase 10 times,

## Myometrium

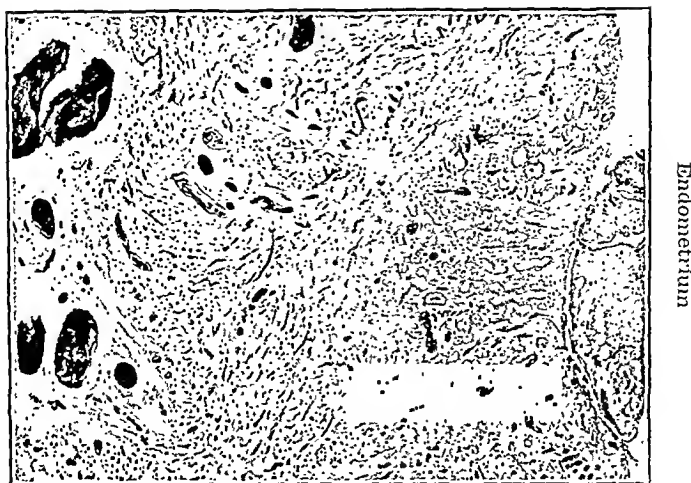


Fig. 1.—Section through uterus of Monkey 604. ( $\times 15$ .) This animal was castrated and then primed with estradiol di-propionate. Injections of the latter were continued, and at the same time, 1 mg. of crystalline progesterone in oil was given daily for twenty days. The animal was then gassed and the arterial system injected with a suspension of India ink. The blood vessels appear as dark black areas on the photomicrograph.

The rich vascularity of both the myometrium and endometrium is easily visualized. In the endometrium, spiral arterioles may be clearly outlined about the glands. In particular, the inner fourth of the myometrium, where the "contraction cones" of Daron are situated, is very vascular.

## Myometrium

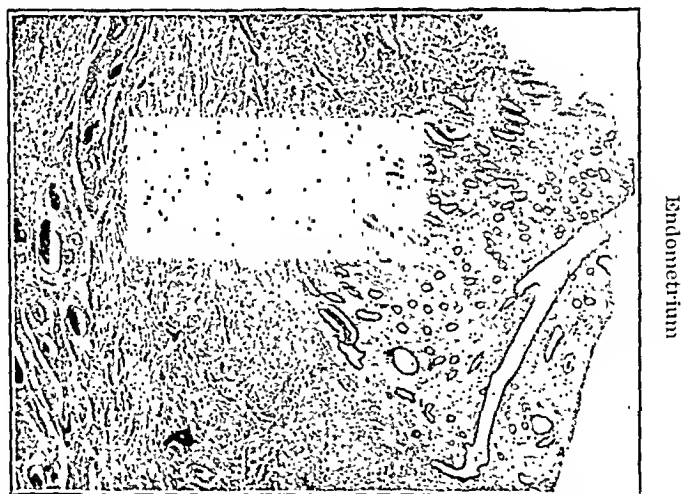


Fig. 2.—Section through the uterus of Monkey 606. ( $\times 15$ .) This animal was castrated and then primed with estradiol di-propionate. Injections of the latter were continued, and at the same time, 1 mg. of crystalline progesterone in oil was given daily for ten days and then 25 mg. of crystalline testosterone propionate in oil daily for the next ten days. The animal was then gassed and the arterial system similarly injected with a suspension of India ink. The blood vessels appear as dark black areas on the photomicrograph.

In contrast to Fig. 1, the uterus here is definitely much less vascular. The stratum vasculare is not reduced in population but in the size of the vessels. The most marked changes, however, have occurred in the inner fourth of the myometrium and the endometrium, whose vascularity is very decidedly decreased.

kidney and ureter were removed for hydronephrosis and ureteral calculi. In 1938 hysterotomy and sterilization were carried out at three months' gestation. Following this procedure, patient developed severe premenstrual cramps which began twelve to fourteen days before onset of flow and continued through most of the period. The flow itself gradually increased until it lasted ten to fourteen days. Pelvic findings were normal.

Beginning the seventeenth day of the next cycle, 10 mg. of testosterone propionate, combined with a bile salt tablet, were given orally each day. Menses began on the thirty-first day. She experienced no premenstrual cramps at all, but had a few at the onset of flow with passage of clots. Flow was profuse for three days and then began to slacken. In order to note whether an increase in flow would result, she was given 10 mg. of testosterone propionate, plus a bile salt tablet, orally. Flow increased several hours later and then began to decrease. The same procedure was repeated two days later with similar results. In review, 10 mg. per day prevented severe premenstrual cramps and dysmenorrhea. Although the flow lasted nine days, it was fairly profuse for only three days, instead of the customary eight to ten days. On the eleventh day of the next cycle (two days after flow ceased), 3 pellets of crystalline testosterone propionate, totaling 25.8 mg., were implanted subcutaneously. (Previous experience indicated that oral therapy gave but temporary results in these cases.) Her next period began on the thirty-first day of the cycle and lasted five days, the flow being fairly profuse on the first two days. She had some mild premenstrual cramps starting a few days before the flow. The following period lasted four days, being profuse for two days. Premenstrual cramps were extremely mild. At present, she is still under observation.

#### SUMMARY

All of the sexual hormones possess bisexual properties to varying degrees. Testosterone, in particular, is not only a powerful androgen, but also a very potent gynecogen. As regards the female, the effects exerted by testosterone are dual, for it may behave as an estrogen or a progestogen.

A physiodynamic explanation is offered of the *modus operandi* by which excessive uterine bleeding is controlled by testosterone propionate. This interpretation is based, in main, upon the response of the myometrial elements to testosterone propionate.

Substantial anatomic evidence is presented to show clearly that the close structural interrelationship between the blood vessels and the muscle fibers of the myometrium is such that adequate contraction of the myometrium will bring about a functional constriction of these vessels, especially the proximal (myometrial) portion of the spiral arterioles. Consequently, the volume of blood flowing to the endometrium, and thus, the amount of uterine bleeding, will be decidedly decreased.

The essential role played by the myometrial elements in controlling the amount of uterine bleeding now becomes manifest. It follows, then, that excessive uterine bleeding will occur if the proximal (myometrial) portion of the spiral arterioles fails to constrict, or be constricted, following the initial extravasation of blood distally. A basic cause, therefore, for excessive bleeding, regardless of the precipitating factor, be it myomas, subinvolution, pelvic inflammatory disease, or merely "functional," is a disruption in the normal hemodynamics of the uterine circulation accompanied by a disturbance in the pattern of uterine contractility at the time of menstruation.

The response of the myometrial elements to testosterone propionate is twofold. First, this hormone will inhibit rhythmic, intermittent

a secretory phase 5 times, and a chronic endometritis once. This makes a total of 30, for 5 of these patients over the course of several years had shown a different type of endometrial picture on separate occasions of excessive bleeding. Two disclosed hyperplasia on one occasion and an interval, non-secretory phase on another. Two were found to have a secretory endometrium and an interval, non-secretory one on separate occasions. One patient had a secretory phase once and endometrial hyperplasia on two subsequent studies. Thus, further evidence is added to show that the endometrial status at the time of bleeding is minor. The only factor that was constant in every case was the myometrium. Logically, therefore, it is to the myometrium that we must look for the factors controlling the amount of uterine bleeding.

Dosage, route, and interval of administration will be discussed in detail elsewhere.<sup>81, 82</sup> Briefly recapitulated, it was found that dosages of 10 to 30 mg. of testosterone propionate would lessen the bleeding materially, while a total dosage of 10 to 120 mg., with a general average of 40 to 60 mg., was necessary to stop the bleeding completely. The initial injection of 10 to 25 mg. of testosterone propionate was given intramuscularly, or else divided between the intramuscular and subcutaneous routes. Subsequent injections, at intervals of two to four days, were given deep subcutaneously in the deltoid region. A therapeutic result was usually obvious in one to four days. Frequently, following a slight initial reduction in flow, an exacerbation of flow may occur. This is transient, usually lasting from three to twelve hours or more. It is practically pathognomonic of a sharp subsequent decrease and rapid cessation of flow. Injections of testosterone propionate should not be given during this temporary increase of flow, for the bleeding may be prolonged over a still longer period of time.

Since spontaneous remission of menorrhagia very frequently occurs, attempts at prophylactic treatment have almost all been confined to the treatment of one or two cycles. If a secretory phase is found premenstrually, from 10 to 30 mg. given in divided *subcutaneous* doses in the seven to ten days before the period will usually be sufficient to control the tendency to excessive flow. If hyperplasia exists, from 50 to 100 mg. given in divided *subcutaneous* doses in the two or three weeks before the expected period will usually suffice.

Two other methods of administration of testosterone propionate were used. These were the oral administration of the hormone (10 mg. tablets) combined with bile salts and the subcutaneous implantation of pellets of crystalline testosterone propionate as a prophylactic measure.

No signs of masculinization were ever noted. In fact, in a personally observed series of over 200 women treated with testosterone propionate for various conditions, no such signs were ever observed. The only possible sign of defeminization was the loss of libido in three patients. It is interesting to note in this connection that nymphomania may be relieved with testosterone propionate.<sup>48</sup>

The following case history will illustrate the oral administration of testosterone propionate plus bile salts as well as the use of pellets of crystalline testosterone propionate.

CASE 1.—A white housewife, aged 30 years, gravida v, para v, came to the dispensary complaining of prolonged, profuse, and painful periods, accompanied by many clots, lasting ten to fourteen days, and saturating an average of 60 double-sized pads per period. Menses began at eleven, recurred at twenty-four to twenty-eight-day intervals, and lasted seven days, always being very profuse. In 1937 right

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MORRISANIA HOSPITAL

## DISCUSSION

DR. WILLIAM H. VOGT, ST. LOUIS, MO.—Recently I had under my care a case of functional bleeding that could not be controlled. This woman then went to another physician and he advised the use of testosterone. The physician who advised this treatment wrote me that he had never seen any masculinization from the use of testosterone. I finally, however, gave it to the patient and she grew a nice little moustache very promptly.

DR. ABARBANEL.—We have not seen any signs of masculinization. This covers a personally observed series of over 225 patients treated for various obstetric and gynecologic disorders. I have seen two patients treated by other men in which masculinization was produced with doses of over 1,000 mg. But this dosage goes back to the pharmacologic discussion as to what constitutes a physiologic dose. One does not have to give huge doses to achieve therapeutic results.

Regarding the moustache Dr. Vogt talks about, it must be remembered that 95 per cent of normal women have some hair on their upper lip. Dr. Vogt would not hesitate to give progesterone, yet this hormone is definitely androgenic. It will produce precocious descent of the testes, hasten the growth of the penis in the immature rat, as well as bring about a marked increase in the size of a guinea pig's clitoris.

uterine contractions, thereby eliminating the pumping action of these movements. As a result, the volume of blood flowing *to*, and thus *through*, the uterus will definitely decrease, for the degree of activity of muscle and its blood supply are directly proportional. Second, the direct stimulative, squeezing effect of testosterone upon the myometrial elements will bring about a functional constriction of the myometrial vessels. The sum total of the twofold effects of testosterone propionate (inhibition of intermittent uterine contractions, direct stimulative action upon the myometrial elements) acting simultaneously upon the myometrial elements will result in a decided reduction in the flow of blood *to* the endometrium. Consequently, the amount of uterine bleeding will be very considerably diminished. Upon these considerations, the use of testosterone propionate for the immediate treatment of excessive uterine bleeding finds its rationale.

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be expected to develop dystocia in labor or who did have unpredicted dystocia were in the selected group. Two hundred and forty-seven were studied ante partum and 153 during labor or in the post-partum period. The 247 had been classified clinically, either as generally contracted, male type pelvis, generally contracted funnel, or as simple flat pelvis. The 153 patients who developed unanticipated dystocia in labor had been diagnosed clinically as having normal pelvis. During the period in which this study was conducted, the operative incidence in clinic cases at the hospital was 10.12 per cent, and the cesarean section incidence was 1.6 per cent.

The types and the frequency with which they occur in this study are shown in Table I.

The incidence of mixed types is shown in Table II.

TABLE I. PURE AND MIXED TYPES WITH PERCENTAGES: 400 CASES

	TOTAL	PER CENT	PURE	PER CENT	MIXED	PER CENT
Gynecoid	224	56.00	113	28.25	111	27.75
Android	95	23.75	50	12.50	45	11.25
Anthropoid	69	17.25	56	14.00	13	3.25
Platypelloid	12	3.00	11	2.75	1	0.25
Total	400	100.00	230	57.50	170	42.50

TABLE II. INCIDENCE OF MIXED TYPES

	NUMBER	PER CENT
Gynecoid	113	28.25
Gynecoid: narrow forepelvis	59	14.75
Gynecoid: anthropoid	36	9.00
Gynecoid: platypelloid	15	3.75
Gynecoid Misc.	1	0.25
Android	50	12.50
Android: gynecoid	18	4.50
Android: anthropoid	18	4.50
Android: platypelloid	9	2.25
Anthropoid	56	14.00
Anthropoid: gynecoid	13	3.25
Platypelloid	11	2.75
Platypelloid Asym.	1	0.25

*Gynecoid Type.*—Two hundred and twenty-four cases were found at the completion of the study to have a gynecoid type pelvis. One hundred and thirteen were the pure type and 111 were of the mixed type. The majority of the patients were small or average in size, but 60 were of more than average size. There were 138 who had been studied ante partum and 86 who are included because they developed dystocia in labor. Twenty-four patients, in the group studied ante partum, developed dystocia, while the other 114 were delivered normally.

*The pure gynecoid type* occurred twice as frequently as any other type. Delivery was spontaneous in 65 of these cases. Inlet dystocia, requiring cesarean section, developed in 9 patients in whom the pelvis was small or of average size, yet only one had an anteroposterior diameter below 10.5 cm. Oversize of the fetus was a factor in the disproportion in the majority. Arrest of the head at or below the level of the spines of the ischium took place in 39 patients. In this group the side wall convergence was greater and the interspinous diameter nearly 1 cm. less than in the group that delivered spontaneously. In 19 of the 32 patients requiring midforceps delivery, the occiput remained persistently posterior or in transverse arrest. Prolonged labor occurred in all of the cases in this latter group, the average in

## STEREOROENTGENOGRAPHY OF 400 PELVES WITH CLINICAL CORRELATION\*

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MANY methods of roentgen pelvimetry which give accurate measurements of the internal diameters of the pelvic inlet have been perfected in the past few years. In skilled hands they have been of great value in estimating disproportion between the fetal head and the inlet, but most methods of pelvic radiography have been disappointing to the clinician, seeking a way to solve the problems of difficult labor and disproportion below the level of the inlet. Although techniques have been greatly simplified, they have never received widespread use in clinical obstetrics. The studies of Caldwell and Moloy<sup>1</sup> on the variations in shape and size of the female pelvis have stimulated renewed interest in pelvic roentgenography in the hope that more frequent prognostication of dystocia may result from the use of the technique they propose. Caldwell and Moloy have classified the pelvis in 5 types, the gynecoid, the android, the anthropoid, the platypelloid and the asymmetrical. In each type distinctive anatomic features in the posterior segment of the inlet, in the sacrosciatic notch and in the subpubic arch are present together with varying degrees of convergence of the side walls and variations in the inclination of the sacrum, which influence the shape and size of the pelvic inlet and outlet. In 1933 Moloy<sup>2</sup> perfected a method of viewing films through a specially constructed precision stereoscope. Stereorocutgenograms of the inlet, a lateral view of the sacrosciatic notch and a view of the subpubic arch are necessary for a complete study when this technique is employed. The inlet stereoroentgenograms viewed through the stereoscope reproduce a phantom image of the pelvis, reveal its configuration, and make direct measurements of any pelvic diameter possible. Employing this method Caldwell, Moloy and D'Esopo<sup>3</sup> were able to estimate the frequency with which each pelvic type occurred and to show that a mixture of the primary types was frequent, the posterior segment of the pelvic inlet of one type being associated with the anterior segment of another type, and also to show from measurements that they may occur in large, average, or small size.

In an effort to determine where in the bony pelvis dystocia occurred and the types of pelvis in which it did occur, the technique proposed by Moloy was used to study the pelvis in 400 women at the Providence Lying-In Hospital. Since the incidence of dystocia in ward cases was low, a selected group occurring in the course of 8,873 deliveries between March 1, 1936, and March 1, 1939, was chosen for study. One hundred multigravida having a history of difficult labor in previous deliveries, and 300 primigravida who, from clinical examination, might

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*Anthropoid Type.*—This type was found 69 times, 56 in pure form and 13 in mixed form. Of the 36 patients studied ante partum 6 developed dystocia. Thirty-three other cases are included that developed dystocia in labor. The anthropoid type is generally adequate in all its internal diameters, even though there is relative transverse narrowing of the pelvic brim. In typical form the average transverse was 12 cm. and in the anthropoid with gynecoid tendency it was 12.4 cm. In 5 cases only was the transverse 11 cm. or less. Marked side wall convergence and a sharp subpubic angle were present in all but 10 cases, and the outlet diameters were the smallest found in any type. The average interspinous diameter was 9.6 cm. and the intertuberosus 9.9 cm. Inlet dystocia was uncommon but arrest of the head low in the pelvis occurred 25 times. The head most frequently descended through the pelvis obliquely posterior and became arrested at the level of the ischial spines.

Many of the cases that had a spontaneous delivery had no difficulty in rotating from a posterior position, because the backward curvature of the sacrum was more marked, giving a wider posterior segment low in the pelvis.

In the mixed form, operative interference was necessary 10 times for the same indications as in the typical form.

*Platypelloid Type.*—This type was found 11 times in typical form, once as an asymmetrical flat pelvis, 15 times as gynecoid with platypelloid tendency, and 9 times as android with platypelloid tendency. The pelvic inlet offered the chief difficulty to descent. The subpubic arch was well rounded and the side walls parallel. The diameters in the lower pelvis were wider than average. In the parent type, dystocia at the inlet occurred 4 times for which cesarean section was done. In three of these, the conjugata vera was 8.8 cm. or less. Midpelvic arrest occurred 4 times.

Mixed types occurred 25 times and 14 of this group had normal, uncomplicated delivery. In 7 dystocia at the inlet occurred, and in 4 cases, arrest of the head at a low level in the pelvis made delivery by midforceps necessary.

TABLE III. DELIVERY IN PELVIC TYPES

	TOTAL	SPONTANEOUS VERTEX	SPONTANEOUS BREECH	LOW FORCEPS	MIDFORCEPS	CESAREAN SECTION	VERSION AND EXTRACTION	BREECH EXTRACTION	VAGINAL HYSTEROTOMY	NUMBER OPERATED
Gynecoid	113	63	3*	6	32	9		1		48
Gynecoid: narrow forepelvis	59	27	2	6	16	6		1	1	30
Gynecoid: anthropoid	36	11	1	1	18	3		2		24
Gynecoid: platypel- loid	15	8	1*	0	2	5		0		7
Gynecoid Misc.	1	0	0	0	0	1		0		1
Android	50	19	1	0	14	12	3*	2		31*
Android: gynecoid	18	7	0	1	5	4		1		11
Android: anthropoid	18	4	0	0	8	4		1	1	14
Android: platypelloid	9	6	0	0	2	1		0		3
Anthropoid	56	25	2	2	23	4		0		29
Anthropoid: gynecoid	13	3	0	0	9	1		0		10
Platypelloid	11	3	0	0	4	4		0		8
Platypelloid Asym.	1	0	0	0	0	1		0		1

\*Twins.

Table IV is a summary showing the type of pelvis and where arrest occurred and indication for delivery.

*Conjugata Vera.*—Estimation of the length of the conjugata vera from the diagonal conjugate has been an important part of clinical pelvimetry, although it is recognized that the method is frequently unreliable. Clinical classification of contraction has depended on finding a conjugata vera of 10 cm. or less. While

the patients with transverse arrest being forty hours and in those with the occiput posterior over twenty-two hours. There was a 10 per cent increase in operative delivery in small- over large-sized pelvises. The pure gynecoid type of pelvis, with its rounded inlet, wide subpubic arch, and average-sized sacrosciatic notch has been considered to be the normal female pelvis; yet it was found in this selected group that prolonged labor (over twenty-four hours) occurred in 30 cases, and that operative delivery was often difficult without evidence of bony disproportion being present.

The lower pelvis was considerably modified when the gynecoid type was associated with a narrow fore pelvis. The subpubic arch was narrower than in the pure form, side wall convergence was more marked, and, as a result, the lower pelvic diameters were considerably shorter. The pelvis in general was of small or average size. Inlet dystocia occurred in 6 of the patients, and arrest in labor at the level of the ischial spines was frequent, occurring in 24 cases. Very few in this group were recognized clinically as patients that might develop dystocia. Twenty-two were multiparas with a history of one or more difficult operative deliveries in previous labors; of these, 12 again had difficult labor requiring operative assistance. This proved to be a dangerous type of pelvis, possessing many of the characteristics of the android. Labor was frequently prolonged and vaginal delivery with forceps was often very difficult.

The gynecoid pelvis when associated with the anthropoid type of forepelvis was found to be of large or average size in three-fourths of the cases, yet prolonged labor was frequent. The narrow subpubic arch that is characteristic of the anthropoid pelvis was found in more than two-thirds of these cases, and it was associated with marked side wall convergence, producing much shorter diameters in the lower pelvis than are usually found with the gynecoid inlet. Arrest of the fetal head at the pelvic brim was uncommon but low pelvic arrest occurred in more than half the cases. The narrowing in the lower pelvic diameters and the sharper subpubic angle undoubtedly aid in part in producing dystocia in this type of pelvis.

*Android Type.*—This type of pelvis was found 95 times, being the second most frequent in the study. It was in pure form in 50 cases and in mixed form in 45 cases. Sixty-six women with android type pelvis were studied ante partum, because it was thought difficult labor was probable from the clinical findings, but 37 of these delivered spontaneously, although labor was frequently prolonged. Also included in this group are 29 patients who developed dystocia in labor. Stereoroentgenograms taken in the puerperium showed the android type pelvis.

In the pure android type, 12 were small, 15 average, and 23 large-sized pelvises. The conjugata vera in pure android averaged 11 cm., but because the inlet had a wedge-shaped form, dystocia was frequent at that level. In very few instances was the head engaged at the onset of labor and the first stage was prolonged as the head descended transversely to the level of the ischial spines. Progress was difficult to judge and delay at the lower levels of the pelvis was just as frequent as at the inlet. The average duration of labor was longer than in any other type, being over twenty-two hours. Definite narrowing of the subpubic arch was found in all cases and convergent side walls in all but 7 of the cases. The average interspinous and intertuberosus diameters were 10.3 cm. and 10.6 cm. Disproportion was twice as frequent at the inlet as in the pure gynecoid pelvis. Twelve cesarean sections were necessary for arrest at the inlet, because the head was unable to adjust itself in a manner to permit descent. Dystocia in the lower pelvis occurred 18 times.

Available space low in the pelvis was limited by the convergence of the side walls and the forward curve of the sacrum which shortens the posterior segment. For this reason forceps delivery was often a difficult procedure. Clinical pelvimetry in android type pelvis is misleading and inadequate. Stereoroentgenograms are especially valuable as the shape of the inlet and the configuration of the mid-pelvis can be detected only by this means.

Dystocia in the mixed forms of android was frequent, being especially common in the android with anthropoid tendency where outlet narrowing was marked.

way than were those of Heaton,<sup>4</sup> Steele and others,<sup>5</sup> Pettit and others,<sup>6</sup> or Rappaport and Seadron,<sup>7</sup> the percentages of the various types approximate their findings and those of Caldwell, Moloy and D'Esopo,<sup>3</sup> and agree with a consecutive series of cases at the Providence Lying-In Hospital taken subsequent to this study.

A prognosis of dystocia based upon clinical pelvimetry alone proved to be inadequate. In this study only 25.5 per cent of the pelvis considered to be contracted clinically, actually developed dystocia. Conversely, it is our experience that abnormal pelvis were frequently difficult to diagnose clinically and often give rise to unexpected dystocia. While roentgenography may give warning that difficulty can arise in labor, it proved reliable for prognosis in only a small number of cases. Spontaneous deliveries have occurred often where difficulty was expected both from pelvic configuration and measurements. Elective cesarean section was performed but once on the basis of the x-ray findings alone. This was in a case with extreme outlet contraction. We have preferred to give an adequate test of labor in all other cases where disproportion was suspected. There is great danger that too much reliance will be placed on the roentgenologic examination by the inexperienced obstetrician. To use this method most successfully cooperation of the roentgenologist and obstetrician is essential for the proper evaluation of dystocia. It should prove to be of most value when the obstetrician acquires a knowledge of stereoroentgenography and uses it to supplement his clinical experience.

The influence which the form of the pelvis has in producing dystocia can be shown with stereoroentgenograms. The variations in the shape of the inlet that can be demonstrated and the importance that convergence of the side walls has in producing lower pelvic contraction is clearly revealed. In the android pelvis, the wedge-shaped inlet, even though its dimensions may be large, explains many cases of arrest at the pelvic brim. The head is unable to enter the inlet because the widest transverse diameter is so far posterior, and the forepelvis is so angulated that it is obstetrically useless. Increased side wall convergence and the forward curvature of the sacrum shorten the lower pelvic diameters and are frequent factors in producing dystocia at the pelvic outlet. In the anthropoid pelvis, transverse narrowing often delays the proper adjustment of the fetal head to the long anteroposterior diameter of the inlet, and the shorter outlet diameters frequently arrest the head in the posterior position at the level of the spines of the ischium.

In the platypelloid pelvis, dystocia at the inlet in our patients was caused by cephalopelvic disproportion due to a short conjugata vera.

The narrow forepelvis and a sharp subpubic angle are important in producing dystocia in the mixed gynecoid forms as well as in those of the android and anthropoid type. One hundred and thirty-nine patients in this series who had dystocia were found to have a smaller retropubic angle, and a sharp subpubic angle associated with increased convergence of the side walls. In the group of 100 multiparas studied because of previous difficult labor, 36 again required operative assistance and 28 of these had a type of pelvis with a sharp subpubic angle and a narrow forepelvis.

TABLE IV

	GYNECOID	GYNECOID NARROW FORE P.	GYNECOID ANTHROPOID	GYNECOID PLATYPELLOID	GYNECOID MISC.	ANDROID	ANDROID GYNECOID	ANDROID ANTHROPOID	ANDROID PLATYPELLOID	ANTHROPOID	ANTHROPOID GYNECOID	PLATYPELLOID	PLATYPELLOID ASYMMETRICAL	TOTAL
Inlet arrest														
Cesarean section	9	6	3	5	1	12	4	4	1	4	1	4	1	55
Midpelvic arrest	10	10	10	1		9	1	4		17	6	2		70
Persistent posterior														
Transverse arrest	9	5	1	1		2	1		2		1	1		23
Breech extraction	1	1	2			2	1	1						8
Version and extraction						3*								3*
Cervical dystocia		1						1						2
Outlet dystocia	19	7	8			3	4	4		8	2	1		56
Total operations	48	30	24	7	1	31	11	14	3	29	10	8	1	217
Fetal deaths	3	2	3	0	0	7	3	2	0	0	0	0	0	20

\*Twin.

a short conjugata vera usually indicates that the pelvis is small, it does not always mean that dangerous dystocia will follow. The size of the fetus is important in these cases. It would seem, however, that the variations in the shape of the inlet, even when no actual cephalopelvic disproportion exists, may prove of the greatest importance. There were 43 patients who had a conjugata vera of 10 cm. or less. It was found 10 times in the gynecoid type, 18 in android, and 12 times in the platypelloid type; 17 patients in whom it was between 9 and 10 cm. delivered normally, and 9 in the same group were delivered with low or midforceps, while 11 patients required cesarean section. In 6 patients with a conjugata vera between 8 and 9 cm., 4 required cesarean section, 1 delivered normally, and 1 was delivered with midforceps. In each type pelvis, cesarean section was performed 5 times.

*Fetal Deaths.*—Eight stillbirths and 12 neonatal deaths in which bony dystocia was a factor occurred in the 400 cases. Eight deaths were associated with the gynecoid type pelvis and 12 with the android type. In 15 cases in which fetal death occurred the labor was prolonged over twenty-four hours. Cerebral hemorrhage occurred in 9 cases. Asphyxia was the cause of death in 5 cases where version and extraction or breech extraction was the method of delivery. Intra-uterine asphyxia associated with hard labor caused death in 6 cases. The type of pelvis played an important part in the deaths in 17 of the cases. These pelvises had a narrow subpubic angle and some degree of outlet contraction. Operative delivery was often difficult because of the funnel tendency. We have noted elsewhere in the paper that the narrow subpubic arch is frequently associated with difficult labor, and it has also been noted by Pettit<sup>6</sup> as a factor in producing dystocia.

## COMMENT

Stereo-roentgenographic study of the pelvis has revealed the variety of shapes that the female pelvis may assume and makes a more accurate classification possible, particularly through the recognition of the many mixed forms. Although our cases were selected in a different

sweeping a statement, for I am sure I have recognized by vaginal palpation diameters inadequate to pass the fetus successfully.

Dr. Walsh clearly states the limitations of x-ray pelvimetry when he says the size of the fetus is important and that the x-ray fails to help us at all on the type of labor we may expect or the moldability of the fetal head.

DR. J. BAY JACOBS, WASHINGTON, D. C.—The technique of pelvic roentgenography has never received widespread use in clinical obstetrics. To me, this is an indication that many obstetricians do not consider it a reliable procedure. Also, they may have come to doubt its value, because too much dependence has been placed upon the inexperienced opinion of the roentgenologist. The obstetrician should himself be familiar with an accepted, simple technique, which he must direct the roentgenologist to follow. The interpretation of all films and the prediction of prognoses should be the duty of the obstetrician.

Dr. Walsh has made it clear that relatively small proportion of the patients in whom difficulty might be expected, actually develop dystocia. This should not underrate the importance of such study in your opinion, because it merely means that the range of observation is such as to detect almost all potential abnormalities rather than overlook any.

For the benefit of men who have not employed x-ray for pelvic mensuration or prognostication, I should like to differentiate between some of the commonly used terms and procedures.

Until recently roentgen pelvimetry was concerned principally with the pelvic inlet, which in my opinion is still and shall always be the most common seat of dystocia. With the use of a single film, we have been able to observe the contour of the inlet, and determine its measurements, as well as anticipate the mechanism of engagement. The value of this procedure is evident.

After Caldwell and Moloy called attention to pelvic architecture, especially as viewed from the lateral aspect, I instituted a technique of lateral pelvimetric roentgenography. This procedure is simple, rapid, accurate, and requires only one film. So much information may be obtained, that in my opinion, every borderline case warrants such study.

In 1929 Johnson described his technique of stereoroentgenometry. By this means, two views are made of the same object, just as it would be seen by each of your two eyes separately. Utilizing the two films and his apparatus known as the stereoroentgenometer, the points designating pelvic diameters may be located in space, and the distances between them may be readily measured. This impresses me as being the most accurate method of pelvimetry, although the technique is too complicated for general use.

By stereoroentgenography is meant the placing of two stereoscopic films in the stereoscope, and the actual visualization of the pelvis in three dimensions. Should the precision stereoscope be used, one may be able to measure pelvic diameters in space. This is a refined procedure, but it necessitates expensive apparatus, and as employed by the author, requires four films for one complete pelvic study. Besides the disadvantage of expense, which is frequently a factor, many other items must be considered.

After studying several hundred lateral pelvigrams, I have come to the conclusion that the true conjugate diameter is still the most important pelvic dimension, and that it bears no definite relationship to the diagonal conjugate. I take my pictures in the standing posture, and have observed that in the vast majority of instances the head tries to engage with the biparietal diameter in the true conjugate.

DR. GEORGE F. PENDLETON, KANSAS CITY, Mo.—I am particularly impressed with what you and I call the simple contracted pelvis in the gynecoid type. We in Kansas City are in a city, almost wholly American, but we do see a lot of simple contracted pelvises which would still go in the gynecoid group. If a measurement is made early and again in the latter part of labor, you will sometimes be surprised how it has increased in size. It is an important practical point that we make use of quite often.

It is more difficult to understand what the causes of dystocia are in some of the pelves of the pure gynecoid type. Oversize of the fetus in the small and average-sized pelves accounts for the majority of cases of inlet dystocia in this study. We have noted a slight decrease in the lower pelvic diameters in cases of outlet dystocia, but equally large babies were delivered normally through similar or smaller diameters.

There are many pelves in which bony obstruction does not account for all the difficulties encountered. Unyielding soft parts, ineffectual expulsive forces, and the ability of the fetal head to mold easily, all have an important bearing on the successful culmination of labor and have to be considered in estimating the factors that produce dystocia.

Stereoroentgenography has been a great aid in the management of patients requiring operative intervention. It emphasizes the danger of using a routine method of procedure when forceps delivery is necessary in pelves which are not uniform in shape. We have attempted to use the most advantageous pelvic diameters for traction and the proper levels at which to attempt rotation. As a result, the frequency of difficult forceps delivery has been greatly reduced.

#### CONCLUSIONS

1. Classification into type has been found to be accurate and adequate for clinical use.
2. Stereoroentgenography helps explain many of the causes of dystocia.
3. The information gained by the use of this method has been valuable in selecting the best type of operative procedure.
4. Although it is a valuable adjunct to our armamentarium, it cannot supersede clinical experience.

We wish to express our gratitude to Dr. Bertram H. Buxton, Chief of Staff of the Providence Lying-in Hospital, under whose supervision this study was conducted, and to Dr. Russell R. Hunt, the Roentgenologist at the Hospital, for his cooperation.

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#### DISCUSSION

DR. ROBERT L. DENORMANDIE, BOSTON, MASS.—Does x-ray pelvimetry tell us more than intelligent clinical study does? Unquestionably in some cases it will. Is diagnosis of probable dystocia so certain by x-ray that we can rely on it implicitly? Dr. Walsh answers this very clearly and honestly. Even in the pure gynecoid type, the normal female pelvis, he found labor often prolonged and operative delivery often difficult. In only one case did Dr. Walsh do an elective section because of x-ray finding and that because of extreme outlet contraction. I am sure he would have done the same without the help of the x-ray.

Dr. Walsh states that clinical pelvimetry in the android type pelvis is misleading and inadequate, and that the shape of the inlet and configuration of the mid-pelvis can be detected only by stereoroentgenograms. That seems to me a bit too



TABLE I. INCIDENCE OF THYROID TISSUE IN TERATOMAS OF THE OVARY

	TERATOMAS AND DERMOIDS	WITH THYROID TISSUE	PER CENT
Meigs	27	2	7.4
Pick	21	6	28.5
Rohdenburg	61	9	14.7
Shaw	23	5	21.7
Spencer	66	1	1.5
	198	23	11.6

Gottschalk in 1899 is said first to have described the tumor under the diagnosis of folliculoma malignum ovarii. Later Kretschmar described a similar tumor which he at first called an endothelioma and later a thyroid metastasis. Pick in 1902 is credited with first recognizing the tumor as thyroid tissue.

Several explanations of the source of the thyroid tissue in the ovary have been advanced. Metastases from a normal or an adenomatous thyroid and metastases from carcinomas of the thyroid are opinions that have now been discarded by pathologists. It is certain that most of the tumors described are teratomas because of the presence of other types of tissue. The pure thyroid tumor of the ovary is believed to be a unilateral development of a teratoma.

The argument of Bauer that struma ovarii is not thyroid tissue but a colloid degeneration of pseudomucinous cystadenomas is refuted by several facts: (1) the morphology and stain-reaction of the tumors are similar to thyroid gland tissue; (2) the chemical examinations have showed the presence of iodine in some and the absence of pseudomucin in all tumors examined (Plaut); (3) the feeding of tadpoles with tumor tissue or with thyroid gland produces precocious growth and development (Plaut).

#### CLINICAL SIGNS AND SYMPTOMS

There are no clinical symptoms or signs that can be depended upon to differentiate a struma ovarii from an ordinary teratoma. It is said that ascites is a common finding. Only three cases (Kovacs', Kleine's, Moench's) have been reported which showed any suggestion of hyperthyroidism relieved by the removal of the ovarian tumor. Several patients had struma of the neck. One patient developed a mild hyperthyroidism following operation (Trapl's).

The great majority of the reported cases were clinically benign. A few of the patients remained well five or more years following operation, but most of the follow-up reports are incomplete and cover too short a time to be of much value.

Several cases were definitely malignant. Werth found metastases in the peritoneum of the bladder and anterior rectal wall. Shapiro found omental metastases. Boxer's patient died five years after operation of metastases in the liver. Proescher and Roddy's patient (Case III) died five months after operation and had metastases in the liver, mesentery, and omentum. Kretschmar's patient died less than two years after operation of probable recurrence.

#### CASE REPORT

Miss L. M. O., aged 26 years, white, was referred by Dr. Reuben Johnson, Jan. 16, 1937. For the past six to eight months she had had a heavy feeling in the lower right abdomen when she ran to catch a streetcar. Two weeks before she was examined she had noticed a hard lump in the right side of the lower abdomen. She thought she had a "rupture." There had been no other symptoms.

Menstruation began at age 13 and had been regular about every thirty days. The flow had been normal in amount, lasting three to four days and painless.

DR. FREDERICK H. FALLS, CHICAGO, ILL.—There is no question that pelvic measurements change from early pregnancy to the end of pregnancy, and particularly during labor. We forget that the pelvis is made up of numerous joints and that during pregnancy those joints are softened.

DR. WILLIAM T. McCONNELL, LOUISVILLE, KY.—It is chiefly of academic value to know the pelvic measurements when labor sets in. What we want to know is whether or not that particular head can easily go through that particular pelvis at that particular time. Now there is a whole lot we can tell without x-ray. I do not know how one can tell all there is to be known, however, unless he is himself familiar with some x-ray technique.

DR. LEROY A. CALKINS, KANSAS CITY, MO.—I would like to ask Dr. Walsh if he has taken any x-ray pictures of the inlet contractions with the woman in the Walcher position? Has he also taken any pictures of the outlet contraction with the woman in the exaggerated flexion of the thighs on the abdomen position?

In our clinic more than 90 per cent of all cases of dystocia are due to poor labor pains, again bringing in the point that perhaps it is an endocrine dystocia and not a pelvic dystocia. Dr. Walsh's figures would indicate, by implication at least, that such might be the case.

DR. WALSH (closing).—This method of study of the pelvis is admittedly expensive. We were trying to get acquainted with this form of x-ray pelvimetry, and we began by studying cases ante partum to acquire some knowledge of the configuration of the pelvis. We have made only a few measurements in labor.

I do think that a knowledge of stereoroentgenography needs to be acquired by the clinician or the obstetrician, and he can acquire this only by collaboration with the x-ray man.

We feel that as we have gone on, since March, 1939, using this method less frequently, that we use it more successfully because we have now a greater knowledge of the pelvis.

Replying to Dr. Calkins, we have not attempted to see whether there was an increased diameter after change of posture. We do not have the x-ray machine on the delivery floor.

## STRUMA OVARIUM\*

H. M. N. WYNNE, M.D., J. S. MCCARTNEY, M.D., AND  
J. F. MCCLENDON, M.D., MINNEAPOLIS, MINN.

THYROID tissue is frequently found in dermoid cysts and teratomas, either as one of the elements composing these complex tumors or as the predominating tissue. Occasionally an ovarian tumor is composed entirely or almost entirely of thyroid tissue and then is called struma ovarii.

The frequency with which thyroid tissue has been found in ovarian teratomas by various authors is shown in Table I. The marked differences in this incidence as reported by these authors may perhaps be related to the efforts made to demonstrate its presence. In a single section, none of this type of tissue might have been present, whereas multiple sections might have revealed it.

\*Read at the Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 7 to 9, 1939.

tuberosity of the ischium. X-rays of the pelvis showed a destructive bone lesion of the right ischial tuberosity and inferior ramus of the right pubis. X-rays of the chest showed no abnormality (Fig. 1).

Operation was performed Jan. 20, 1939, by Dr. E. T. Evans. Complete removal of the tuberosity of the right ischium and inferior ramus of the right pubis was done. The patient recovered quickly from the operation. A pelvic examination on July 24, 1939, showed no signs or symptoms of recurrence.

The specimen of the ovarian tumor was an olive-shaped mass measuring 9 by 6 by 6 cm. The external surface was for the most part smooth, although there were a few rounded nodular elevations. Gross section showed a variegated appearance. The major portion was composed of spaces filled with firm transparent brown colloid. One



Fig. 3.

Fig. 3.—Photomicrograph of primary tumor of area, showing well-differentiated thyroid tissue with large amounts of colloid.  $\times 300$ .



Fig. 4.

Fig. 4.—Photomicrograph of primary tumor of area, showing adenocarcinoma.  $\times 300$ .

multilocular cyst, filled with clear fluid and measuring 4 by 3 cm., was present. A solid area of pale, yellowish white tissue, apparently made up of coalescing smaller masses, comprised the balance of the tumor mass. No hair, sebaceous material, or mucus was seen (Fig. 2). Slicing into blocks of 5 mm. thickness revealed no appearance other than that noted on the first section.

Microscopic examination of two apparently representative areas showed what appeared to be approximately normal adult type of thyroid tissue, with acini full of colloid. In a few areas there seemed to be some piling up of the cells, but no acinar structures of the type found in exophthalmic goiter were present. In one place there was a suggestion of invasion of a blood vessel. Occasional mitotic figures were found. In no portion was there any type of tissue except thyroid (Fig. 3). The diagnosis was a benign teratoma with a unilateral line of development, only thyroid tissue being present. After the metastatic tumor was found in the ischium, six more blocks were taken from the original tumor for microscopic examination. This examination showed a much more undifferentiated type of thyroid tissue than was present in the first two blocks. In these sections the structure was that of fairly typical adenocarcinoma (Fig. 4). Some solid areas con-

She had never had any intermenstrual bleeding. The last period began Dec. 29, 1936. There had been no change in her periods for several years.

*Physical Examination.*—She was a healthy-looking young woman. There were no abnormalities except a firm, nodular, insensitive, movable mass in the pelvis about the size of a small grapefruit. The cervix and corpus were normal in size but displaced to the left of the midline. No enlargement of the thyroid was made out. No clinical signs of hyperthyroidism or of hypothyroidism could be elicited.



Fig. 1.—X-ray of left ischium, showing metastasis.

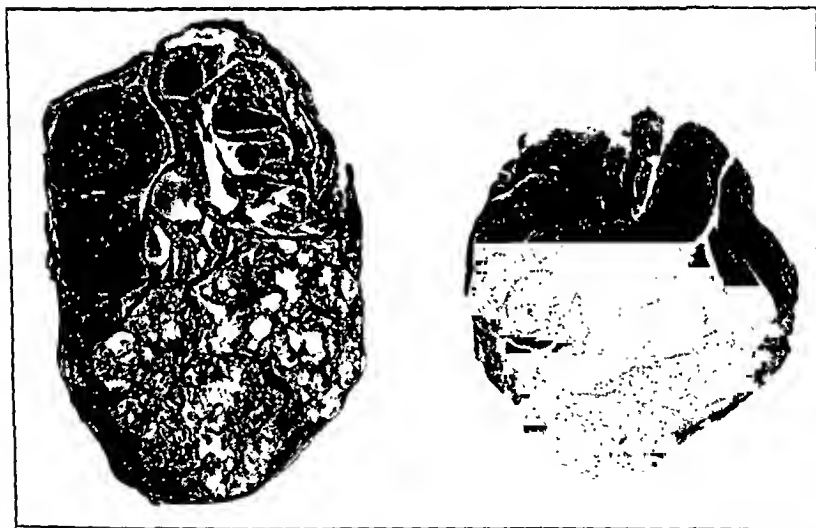


Fig. 2.—Photograph of gross specimen, showing external and cut surfaces.

*Operation* was performed Jan. 22, 1937. A solid, irregularly nodular tumor of the right ovary was removed. There were no adhesions. There was no ascites. Exploration of the abdominal organs revealed no other abnormality. The left ovary was of normal size and appearance. The patient recovered rapidly from the operation and returned to work March 1, 1937.

Pelvic examinations made at intervals since the operation have showed no evidence of recurrence in the pelvic organs.

The patient returned to Dr. Johnson Dec. 30, 1938, complaining of pain in the region of the right knee and right hip. There was tenderness on pressure over the

This long exposure to the action of formalin caused a large amount of iodine to be freed from the protein fraction, but it still appears as total iodine. For purposes of comparison it is to be noted that normal tissue other than thyroid contains about 40 to 80 micrograms of hormone iodine per kilogram (Baumann and Metzger found but from 6 to 60 micrograms of total iodine per kilogram of normal ovary). A certain comparison can hardly be drawn between the analyses of Meyer, Neu, and Plaut, and those made by us of the ovarian and ischial tumors and the values given for normal thyroid tissue. The thyroid hormone values of 5,140 to 28,300 are more like those of thyroid tissue than of nonthyroid tissue. There seems to be no doubt that the thyroid hormone was manufactured in the struma ovarii and ischial tumor and not merely derived from the thyroid gland, as it would be in much smaller concentration if the latter were true. The table shows that the primary tumor from our case contained from 375 to 3,750 times as much iodine as reported by Baumann and Metzger for the normal ovary.

#### SUMMARY AND CONCLUSIONS

An instance of malignant primary unilateral teratomas of the ovary composed entirely of thyroid tissue is reported. The ischial metastasis also contained only thyroid tissue.

At no time was there any evidence that this tumor tissue caused the symptoms of hyperthyroidism or that it substituted for the secretion of the normal thyroid gland.

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#### DISCUSSION

DR. JAMES E. DAVIS, ANN ARBOR, MICH.—It is true that thyroid tissue occurs in teratoblastomas in a frequency of 11 to 12 per cent. Yet this is not a figure of great frequency when one considers that in the group of body tumors teratoblastomas make up only a fair percentage. The frequency of the entire group of teratoblastomas has been given by Miller as 10.9 per cent in a whole group of 21,953 miscellaneous ovarian tumors.

Thyroid tissue in a teratoblastoma will in most instances show numerous areas in which the vesicles are quite immature. The vascular supply is uncertain, and opportunity for irritation of the vesicular epithelium is present. Therefore, one should expect a considerable percentage of these cases to develop ultimately into malignancies. It is very interesting that Dr. Wynne's case showed a metastasis to bone. This is not unusual in tumors of the thyroid gland.

The most attractive explanation of the formation of these tumors is that of the organizer theory which was first defined by Spemann. The organizers are

taining no colloid were found. In none of the eight sections was anything found resembling tissue other than thyroid. A small amount of ovarian stroma and a few follicular cysts were present in one block.

*Specimen of Ischium:* The bone was replaced in an area 6 by 4.5 by 4 cm. by soft shiny gelatinous tissue. It was not slimy. No solid areas were noted. Microscopic examination (Fig. 5) showed a structure readily recognizable as being that of thyroid tissue. It was not quite so well differentiated as that found in the first two blocks from the ovarian tumor but better differentiated than that in some areas of the other six blocks. The ischial tumor might easily have passed for an actively growing benign adenoma of the thyroid gland. No tissue other than thyroid was present in the ischial tumor.

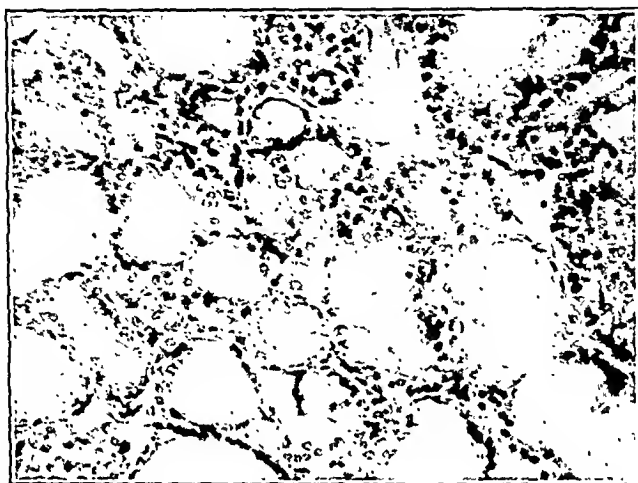


Fig. 5.—Photomicrograph of metastasis in ischium, showing well-differentiated thyroid tissue.  $\times 300$ .

Since it appears from the literature that microscopic examination alone does not suffice for the recognition of thyroid tissue, one of us analyzed the ovarian and ischial tumors by the method of McClendon-Bratton. The results of the tests are shown in Table II.

The apparent discrepancies in the analyses of the ovarian and ischial tumors are doubtless to be explained by the fact that the examination of the ovarian tumor was not made until after more than two years' immersion in 10 per cent formalin.

TABLE II  
(Micrograms per Kilogram)

	TOTAL IODINE		THYROID HORMONE IODINE	
	WET MICROGRAMS	DRY MICROGRAMS	WET	IN DRY PROTEIN FRACTION
Colloid from struma ovarii (2 years in formalin)	22,500		1,310	5,140
Ischial metastasis (2 months in formalin)	9,100		3,230	28,300
Ovary (Baumann and Metzger)	6 to 60			
Struma ovarii				
Robert Meyer		14,000		
Neu		20,000		
Plaut Spec. I		673,000		
II		25,000		
III		00,000		
Normal thyroid (McClendon)		120,000		
		to 5,940,000		

flow out and leave the cervical canal unplugged, frequently allow pregnancy, whereas the low grade type of infection effectually prevents it.

No discussion is here attempted of the variability in chemistry of the mucus plug at different stages of the menstrual cycle for, as yet, proof of absolute and constant variations are not, to my knowledge, available. But, should this factor of chemical variability, with a consequent variability of penetration by the sperm, certainly exist, it still presents no argument against surgical attempts to remove the infected glandular structures. Surely it can be agreed that "mass action," "central stream progress," and kindred observations and beliefs in the rate of progress and method employed by the sperm in traversing the cervical canal, might readily be perverted if the secretion in the canal deviates markedly from the normal.

After an adequate and complete study of the individual case has ruled out all other factors, and when such a chronic and low grade endocervicitis, with its resultant plug, has been repeatedly demonstrated at different phases of the menstrual cycle and therefore believed to be constantly present, I have not hesitated to suggest a coring operation for the removal of the diseased glands.

After employing a number of methods I have reached the conclusion that, in my hands at least, the technique described by Sturmdorf offers more chances for success than any other. Its peculiar virtues, which include the preservation of circular fibers, the covering of the raw surface with healthy mucosa, and the lessened likelihood of disturbing hemorrhage, all recommend it.

The cost in time and money to the patient incident to a surgical procedure of this type is, of course, a factor which may be argued against it, and for this reason I, along with others, have attempted to achieve the same ends by electrical conization. Unhappily, the results have not been satisfactory, and indeed, in a few instances, complications such as hemorrhage, postoperative stricture, infection, and prolonged offensive drainage with delayed granulation have convinced me that Sturmdorf's technique is infinitely preferable.

(I pause here to observe that, since abandoning the coagulation feature after electrical conization, the frequency and severity of hemorrhage has been decidedly lessened.)

I have tried this modified Sturmdorf procedure on 79 selected cases; that is, selected because of the belief that the cervix alone was at fault, with the results that in 63 cases pregnancy followed within nine months; in 7 instances, before the next period was due, in 12, within two months, and the remainder scattered over the above-mentioned period. It may be properly argued that other factors conducive to pregnancy might have been spontaneously injected during a period as long as nine months. I cannot successfully dispute such a conclusion except to offer the evidence that the period of infertility in these 79 cases had varied from four to fourteen years, and that many other procedures had been attempted without results.

Further, I believe that in many cases of barren marriages, untreated, and with spontaneous recovery at and around the menopausal age, the

regarded by Huxley and De Beer as diffusible, labile agents which act upon the area of proliferation in the impregnated ovum about the time of formation of the primitive streak. The general effect of the organizer is to induce neighboring tissues to follow the axial plan of organization.

It is quite interesting in cases of teratoblastoma to look carefully into the family history. Quite recently I had the experience of finding three sisters with teratoblastomas. The mother had similar tumors. The mother's sister and a grandmother gave histories of teratoblastomas, all occurring at approximately the same age. Koltonski and also Luxenberger have reported like experiences.

DR. WYNNE (closing).—The left ovary in this patient was grossly normal. Examinations since the operation have shown no recurrence in the pelvis. The patient was a young woman who hopes to have children.

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## TRACHELOPLASTY (STURMDORF TECHNIQUE) IN THE TREATMENT OF STERILITY\*

OREN MOORE, M.D., CHARLOTTE, N. C.

**A**LTHOUGH increased knowledge of endocrinology and of the physiology of fertilization and conception has increased our success in treating the nonfertile marriage, there is still a large percentage of sterile cases in which the cervix is the offender. In my own practice, it is believed that in approximately 60 per cent of all patients who present themselves for study, sterility may be finally charged against the cervix. This, of course, does not apply to that group which, due to massive pathology and indicated surgery, are obviously, at first glance, hopelessly and permanently out of the picture.

It is not believed, however, that in the surgical cases marked structural changes, stenoses, strictures, and the like are the predominating factors, but rather, that chronic endocervicitis of a glandular origin is to blame. These glands of the endocervix, being charged with the duty of producing mucus for lubricating and protective purposes, and being vulnerable in their location to bacterial attack, respond to the rather frequent incidence of infection by an excess production of tough and tenacious secretion.

This plug of mucus constantly present in the canal offers an effectual barrier to the escape of the sperm from the unfriendly acid atmosphere of the vagina into the more hospitable interior of the upper cervix and uterus for, while the male cell is aggressive in penetration, it is still feeble in power.

Kurzrock has stated that the lytic action of the semen on normal cervical mucus is not duplicated with regard to mucopurulent secretion, and Möench believes that the penetrability of the cervical mucus, by the sperm, varies directly with the viscosity of the plug. I agree entirely with this opinion and believe that I have observed, time after time, that the more acute infections, often with copious fluid discharges which

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\*Read at the Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., September 7 to 9, 1939.



DR. L. A. GRAY, LOUISVILLE, KY.—The stem pessary seems to have fallen into considerable disfavor in recent years. However, at the Johns Hopkins Hospital it has been used steadily for many years and is still being used. We have never seen any infections from it, at least in one or two hundred cases. It is of particular value in antelexion, with the small cervix, allowing not only a large canal but producing hypertrophy of the cervix and uterus.

DR. D. N. BARROWS, NEW YORK, N. Y.—We used to do about 200 Sturmdorf operations a year at Bellevue under Dr. Holden. After perfecting our technique with conization and cauterization, we cut down the Sturmdorf operations to about ten a year.

DR. MOORE (closing).—I have delivered 47 women who have become pregnant after a cervical operation. We have found no difficulty at all with dilatation of the cervix and used no interference. Let me again stress that I was advocating this operation for a mild cervicitis and in nulliparous women. In my experience the Sturmdorf operation is the best of all operations devised for this condition, but it is for the woman who has not had a baby and who has what might be called a clean cervix.

As to Dr. Cron's question about how we discover whether the sperm cells have penetrated the cervical mucus I can say this: When finding them I have never been sure whether I had carried them up with my instrument or not. Our practice is to take a plug of mucus, and put it on a slide with some sperms from the husband. The action of the sperms appears perfectly normal under the microscope until they touch the plug of mucus when they become firmly enmeshed therein. In a short time they will die. If they do this on the stage of the microscope, they also undoubtedly do so inside of the cervix.

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## AN ELECTRIC TIMER AS AN AID IN COUNTING THE FETAL HEART IN THE SECOND STAGE OF LABOR AND IN TIMING AND SPACING FORCEPS TRACTION<sup>\*</sup>

WALTER B. MOUNT, A.B., M.D., F.A.C.S., MONTCLAIR, N. J.

(From the Obstetrical Department, Mountainside Hospital)

THE importance of watching the fetal heart during labor has been stressed so often that its desirability may be granted. A variety of stethoscopes have been designed to facilitate counting the heart sounds, one of which, that of Falls,<sup>1</sup> carries a watch the dial of which is reflected in a magnifying mirror which one can see while listening. However, it was found that the watch cannot be read through the distance segment of bifocal lenses, that the special parts of the instrument are delicate and get out of order or broken, and that the ticking of the watch, intensified by bone conduction, may become annoying.

In 1926 von Wachenfeldt<sup>2</sup> devised a signal clock which rings a bell every fifteen seconds, a bell that one can hear while using a head stethoscope. It is made in Sweden and is run by a dry battery. In 1927 DeLee publicized his electric clock,<sup>3</sup> which rings a bell every fifteen or every ten seconds. The original cost has been reduced, but one must be installed in each delivery room or labor room and all connected with a master clock. We present an electric timer (Fig. 1). It can be connected to any base plug with an alternating current. It is small and light (five inches square and weighing less than two pounds); it can be carried from one delivery room to another, or to another hospital, and can be used in home deliveries. It has not gotten out of order in the four years of its use. The bell can be heard

<sup>\*</sup>Read, in modified form, at the Fifty-Second Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 7 to 9, 1939.

disappearance of the plug of mucus due to the atrophy of glandular tissues (which is a common occurrence at mid-life) results in a physiologic removal of the plug and a consequent opening of the canal.

In conclusion, I hasten to state that so many factors must be considered in a proper study of sterility that one single procedure such as discussed above should not be relied upon too completely; but when one recalls the zeal with which nature maintains the patency of any pre-formed canal, it would seem logical to render her aid and assistance in maintaining this function, and certainly the removal of infected glands of the internal cervix can be so regarded.

#### DISCUSSION

DR. QUITMAN U. NEWELL, ST. LOUIS, MO.—I have always regarded the causes of sterility in this order: first, an endocrine condition where the production of ova was poor. Second, I consider inflammatory changes in the cervix with a ropey discharge as a sterility factor.

I was very much pleased when Dr. Moore said he preferred the Sturmdorf operation for the correction of this condition. I am sure the conization method by the electric knife has its place in the treatment of chronic endocervicitis, but for some years I have resorted to the conical excision method (Sturmdorf) with the cold knife, feeling that the bleeding can be better controlled.

DR. IVAN PROCTOR, RALEIGH, N. C.—Dr. Moore has presented a procedure, which to us has offered very gratifying results, in relieving chronic pelvic disease, and also in increasing the chances of conception.

We divide cervicitis into four groups according to the extent of the disease: (1) Simple erosion; (2) extensive erosion and infection; (3) laceration, erosion, and infection; (4) multiple laceration, hypertrophy, and infection. The first is treated by simple radial cauterization with a thin, flat tip nasal cautery. The second by deep crucial incisions, then more superficial cuts with the cautery. The third by Sturmdorf tracheloplasty. The fourth in sterilized or postmenopausal patients by high amputation. Without preparation I am unable to give statistics on conception following treatment in the first three groups.

DR. HOWARD F. KANE, WASHINGTON, D. C.—In treating cervicitis in sterile patients I have in most cases used linear cauterization. I did that before making any further investigation, before doing the Hühner test, the Rubin test, or investigating the endocrine status of the patient.

Another point in sterility is interesting. I believe that 90 per cent of the women who come to me are the wives of men who are working mentally, young business or professional men, who are worried about their incomes, or their work, and I have been impressed with the large number of cases in which by studying the husband, we have found a somewhat lowered vitality of the sperms. This is almost always found in the mental worker.

It has also been my personal experience to take care of the wives of a number of baseball players. These men are, of course, very active physically, but the strain under which they are working when playing seems to have the same effect as on the men who are worrying about overdue bills, sick patients, etc. I have not seen a wife of a baseball player become pregnant during the baseball season, but they do become pregnant during the winter.

DR. ROLAND S. CRON, MILWAUKEE, WIS.—I would like to learn Dr. Moore's technique used to determine whether or not the sperms have penetrated the tenacious mucus of the cervix; whether he has been able to recover them from the fundal cavity, or whether in the introduction of the instrument to obtain the sperms, the sperms are carried up from below.

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21 PLYMOUTH STREET

## DISCUSSION

DR. SAMUEL A. COSGROVE, JERSEY CITY, N. J.—One must concur in what Dr. Mount says in his discussion of the necessity of watching the fetal heart during the second stage of labor, and in general of what he says as to the proper management of emergencies as indicated by significant variations in the heart rate. In the inexperienced, I have, however, noted undue alarm at transient or insignificant variations in the fetal pulse, and a tendency when they occur to attempt artificial interference under conditions which promise less favorable outcome for the fetus than dependence on the natural further evolution of the labor.

As Dr. Mount has properly pointed out, sometimes nothing can be done to improve the fetal chances. Indeed I would be inclined to think that this is true in most of the situations in which the behavior of the fetal heart causes concern for fetal survival. In many situations one had better resign oneself to the probable loss of the baby than resort inadvisedly to frenzied interference which may carry with it even greater hazard to the fetus, and perhaps definite danger to the mother.

Dr. Mount has been kind enough to permit me the use of two models of his timing device. Our delivery rooms are, however, each equipped with an electric clock, with a separate large second hand, jumping not at intervals of several seconds, but each second. We have found that the timing is more readily done by watching the second hand on these clocks than by the gentle musical note sounded by the device presented by Dr. Mount. This sound may frequently be lost in the variety of noises which may occur in the delivery room.

DR. FREDERICK H. FALLS, CHICAGO, ILL.—I am not in entire agreement with Dr. Mount's statement that rapid heart tones should not cause much concern. Heart tones above the normal maximum of 160 should be the object of close and repeated observation. Richardson has shown an interesting curve in the fetal heart rate in cases of incomplete separation of the placenta. The rate gradually increases up to 180 to 200 in the early stages of separation and as the separation becomes more complete the tones gradually become slower and weaker immediately preceding the death of the baby. I have confirmed this personally and have repeatedly operated in the early stage of the separation, while the heart tones were still rapid, and have secured a living baby.

Some years ago I devised an instrument which I labeled the vaginal stethoscope. I found that hearing and counting the fetal heart tones by placing the ball of the stethoscope against the lower uterine segment through the anterior vaginal wall was practical. The heart tones thus heard about the fourth lunar month are quite clear and strong but one must wait until the fetus turns within the uterus in such a way as to bring the back into apposition with the lower uterine segment.

DR. MOUNT (closing).—I should have mentioned Dr. Richardson's observation of the increasingly rapid fetal heart found in early ablatio placentae. It is still true that the rapid fetal heart is less often a sign of distress than the slow fetal heart.

In hospitals equipped throughout with electric timing clocks, no other device is, of course, necessary. Furthermore observation of the fetal heart during labor by another physician or a nurse will usually satisfy all requirements.

easily with a stethoscope in one's ears, yet the sound does not disturb the patient or others, so that often we all have forgotten to disconnect the instrument after a delivery.

By manipulating an arm at the back of our instrument one can at will have the bell sound every fifteen seconds, or every thirty seconds, or every minute. Freed<sup>4</sup> states that the fetal heart should be counted for thirty seconds rather than for only fifteen seconds to insure accuracy. Moreover, in case forceps must be used, with this timer one then can watch carefully the duration of the forceps tractions and of the pauses between tractions. Smellie<sup>5</sup> in 1756 directed to "pull gently during every pain; or if the pains are gone, at the interval of four or five minutes, that the parts may be slowly dilated, as they are in the natural labor." Unless one checks the time carefully when using forceps he is likely to hurry and to reverse nature's rule in the spacing of uterine contractions. For the purpose of accurately timing forceps tractions, the longer intervals in the timer are more convenient than the fifteen-second interval. Our hospital electric clocks do not lend themselves to these uses, because the hands move a whole minute at a time.

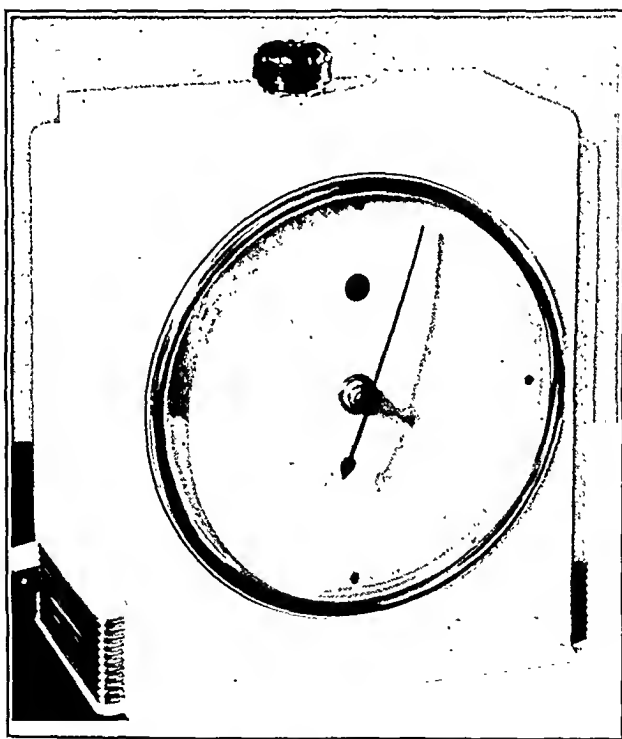


Fig. 1.—Electric timer.

The use of this instrument helps to emphasize and make easier of execution two important points in the management of the second stage of labor which often are slighted to the detriment of the fetus; namely, the frequent counting of the fetal heart and the timing and spacing of forceps tractions.

The fetal electrocardiogram and phonocardiographic records of the fetal heart are not practical late in labor. The various electrical devices for amplifying the fetal heart are expensive and so far not reliable at all times. In a recent survey only two of them were in working order. The DeCosta<sup>6</sup> photostethoscope, the most recent, seems the best instrument of all, in that with each beat of the fetal heart an electric bulb flashes, so that rate and regularity are visible. Few of these devices are now obtainable.

This apparatus is manufactured by Malcolm Woodruff, Montclair, N. J.

dental with the therapy. A blood culture at this time may be of particular value, whereas if taken some hours later it may not reveal the true circumstances at the time of the onset of treatment. We would then have definite information concerning the infecting organism before our therapy has advanced very far. At no time in the past has prophylactic, prompt and accurate bacteriologic investigation of infections in obstetrics and gynecology been so well repaid, as far as the welfare of the patient is concerned, as it is today. Certain exceptions to the above principles must be made for patients in rural areas where laboratory facilities are not available. This excuse, however, cannot be accepted where the real reason is indifference or a lack of administrative or technical cooperation. A guiding principle where adequate laboratory facilities are available should be the early bacteriologic investigation of secretions, discharges or other material where the later possibility of infection seems probable, or at the very latest these studies should be started with the earliest signs of infection. With this information at hand, at the time of the development of a critical condition, the clinician is much better able to decide whether or not specific chemotherapy is indicated without an objectionable loss of time. An example of the application of this principle might be cited, such as taking of vaginal swabs for culture during long labors, at the time of a delivery which is unduly difficult, when completing an incomplete abortion, in patients with recent upper respiratory infections, or at other times when later difficulties seem probable or even possible. It may be well to point out at this time, that it is usually possible to arrive at a probable diagnosis of the presence of hemolytic streptococci in such material, in from five to seven hours and a positive diagnosis in about sixteen hours. It is also of great importance to have frequent bacteriologic investigations after the institution of chemotherapy, to correlate with the clinical course of the disease, for the control of treatment.

Sulfanilamide was the drug used in all patients in this study, excepting those with pneumonia, where sulfapyridine was employed. I have not been greatly impressed with the claimed advantages of other preparations such as prontosil, neoprontosil, benzyl sulfanilamide, sulfanilyl sulfanilamide, etc., over sulfanilamide. Alyea,<sup>1</sup> however, has recently reported the successful employment of sulfanilyl sulfanilamide in a group of male patients with gonorrhea who had failed to respond previously to sulfanilamide. Most German investigators appear to prefer this drug, or those closely allied to it, such as sulfanilyl dimethyl sulfanilamide, in the treatment of gonorrhea. Their results, however, are in general not as good as those here reported. Accordingly, it appears advisable for the present, to utilize only the two preparations mentioned and evaluate the results as thoroughly as possible before proceeding with the use of other related compounds.

It will be noted that the dosage employed is quite varied. In many instances in urinary tract infections, we have employed a low dosage method as first advocated by Kenny and others.<sup>2</sup> In other cases a much larger dosage has been used either experimentally or because control bacteriologic studies failed to indicate a satisfactory result. Where prac-

## CHEMOTHERAPY IN OBSTETRICS AND GYNECOLOGY\*

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(From the Department of Obstetrics and Gynecology, The New York Hospital and Cornell University Medical College)

THE recent introduction of sulfanilamide and related compounds into our therapeutic armamentarium, has revolutionized the present-day treatment in certain diseases of an infectious nature. In a relatively short time many investigators employing animal experimentation, pharmacologic studies, and clinical use by trial and error, have explored some of the actions and uses of the various compounds, in every known form of infection, and in some diseases of a noninfectious nature. Fortunately, the infections influenced the most by the drugs in question have proved to be of relatively common incidence and are diseases for which, with few exceptions, there is no other specific form of therapy available. The practitioner of obstetrics and gynecology is especially fortunate in that several most trying conditions are amenable to this new form of therapy.

An historical review is omitted at this time because of the many frequent reduplications in the current literature. The recent monograph by Long and Bliss<sup>15</sup> contains a chapter with a very complete summary of the historical phases of the development of the various compounds and their uses.

Before proceeding to a detailed analysis of the data in question, I should like to mention two conditions essential, I believe, for successful treatment of patients in this field. The first is that the treatment should be under the complete supervision of the obstetrician or gynecologist, who must assume the responsibility for such therapy. After all, there are many fundamental problems associated with, for instance, the presence of *B. coli* in the urine of the obstetric or gynecologic patient. The problem is not so simple that the consulting internist or "sulfanilamide specialist" can immediately proceed with a plan of therapy. Therefore much knowledge based on our background of experience must be brought into play in deciding on the necessity of therapy, in observing the clinical progress, and in the evaluation of results. It is accordingly of the utmost importance, that all of us, who have these problems to face, should be able to manage successfully our own therapy.

The second point is the all important problem of accurate bacteriologic diagnosis before the commencement of therapy and its control during the period of treatment. There may occasionally be indications in the critically ill patient, for the use of the drug before the nature of the infecting organism is ascertained. Under such circumstances, the bacteriologic investigation can certainly be started, at the latest coinci-

\*Read at a meeting of the New York Obstetrical Society, October 10, 1939.

infections, 86 of whom were obstetric, and 29 gynecologic; 34 patients had gonorrhea, 20 puerperal or postabortal infections, 7 pneumonia, and 4 miscellaneous infections. Included in this latter group, there are one case of lymphogranuloma venereum and one patient with subacute bacterial endocarditis. We have not had an opportunity of evaluating the results in gonorrheal ophthalmia in the newborn, Welch's bacillus infections, or in chancreoid disease. It may be of interest to know that well over 2,000 specimens were studied in our bacteriologic laboratory, for the diagnosis and control of treatment, in the cases here reported.

All patients were treated in the Hospital as bed patients, with the exception of a few with chronic urinary tract infection who were treated by means of one or more courses of small dosage, consisting of 1.5 gm. per day for five days, while attending the Out-Patient Department. Unless some reason to the contrary existed, all medication in the hospital was given at four-hour intervals, both by day and by night, combined with an equal amount of sodium bicarbonate. Blood hemoglobin estimations and the white blood count were done on all hospital patients at least every second day. The drug concentration in the blood, and the urine if indicated, was done at similar intervals. An attempt was made to control the fluid intake, unless contraindicated by fever, so that the urinary output would approximate 1,000 c.c. per day. No dietary restrictions were employed. Nicotinic acid, as advocated by McGinity,<sup>10</sup> was used with some apparent success in a number of our recent cases in an attempt to eliminate some of the minor toxic symptoms. Consideration of the efficiency of renal function was a preliminary prerequisite to therapy. As far as I am aware, renal insufficiency or anemia never deterred us from giving the drug. Other necessary medication was used when indicated. Transfusions were not deferred if thought advisable.

A description of the laboratory procedures employed is omitted for purposes of brevity. Suffice it to say that the studies were instituted as soon as possible after the material was obtained, and every effort was made to identify promptly and accurately the organisms associated with any given infection.

#### URINARY TRACT INFECTIONS

Tables I to XI are self-explanatory. The clinical and laboratory data in each group of patients as well as results of treatment are clearly shown. The results of sulfanilamide determinations in the blood and urine are not included in the tables. In general where "small" dosage

TABLE I. BACILLURIA\* OF PREGNANCY (SULFANILAMIDE THERAPY)

Ante partum		13
Previous urinary tract infection	6	
Urinary tract symptoms	7	
Post partum		44
Previous urinary tract infection	12	
Urinary tract symptoms	32	
Total		57

\*Pus in urine and positive culture but not necessarily febrile.  
455 cultures studied, an average of 8 per patient, variation 2-24.

tial, the dosage has been decreased or stopped before the patient received relatively high or protracted dosage. The avoidance of serious toxic manifestations, particularly agranulocytosis, appears to be largely possible by not unnecessarily prolonging the treatment or by not giving too high dosage. The discontinuance of the drug with the development of "drug fever" is usually indicated. Colebrook<sup>3</sup> very recently reviewed 41 reported cases of agranulocytosis. It is significant that the average dose of the drug in these cases was 48 gm. and in only two cases was the total dosage less than 30 gm. Other observations of importance were the facts that the average duration of treatment was twenty days and that many of the victims were those that received repeated courses of therapy. These considerations may well be borne in mind, especially when treating conditions that are not likely to lead to a fatal outcome. At the same time adequate dosage to maintain a satisfactory blood level or urine concentration must be maintained for a prompt therapeutic response.

In pregnant women at term, sulfanilamide, owing to its marked diffusibility, has been shown by Speert<sup>9</sup> to pass the placenta and invade the fetus in concentrations relatively similar to that of the maternal organism. As far as I am aware no untoward effect on the infant has so far been reported. Speert, in a recent experimental study, found a deleterious effect on the offspring of rats where the mother was given the drug throughout pregnancy. Maternal milk also contains the drug in concentrations considerably higher than the blood, but again no untoward toxic signs or symptoms in the nursing infant have been reported.

In the analysis to follow it will be noted that no mention is made of the use of the drug prophylactically in obstetrics, in an attempt to reduce the incidence of intra-partum or puerperal infection. Such use under certain conditions has been suggested by LaComme,<sup>21</sup> Colebrook,<sup>4</sup> Merlin,<sup>5</sup> Johnstone,<sup>6</sup> Hoare<sup>7</sup> and others. As I have previously shown,<sup>8</sup> less than 1 per cent of puerperal infection in our service is due to the beta hemolytic streptococcus, and only between 2 and 3 per cent is due to a beta strain. In other words, considerably less than one patient out of every 1,000 is likely to develop a beta hemolytic streptococcus infection. This small incidence, to my mind, does not warrant the routine prophylactic use of the drug. There may occasionally be circumstances surrounding a given patient, such as a recent hemolytic streptococcus infection, or the patient has been in contact with such infections. Then the prophylactic use of the drug may be indicated. There has been, however, no work as yet that proves conclusively the value of the drug when given prophylactically.

The present study is based on an analysis of 180 patients treated during the past three years in the New York Lying-in Hospital. The majority of the patients, however, were cared for during the past one and one-half years. The relative importance of the various indications for the use of the drug may be judged by an analysis of the clinical material herein reported. There were 115 patients with urinary tract



The results in general when analyzed are not quite as successful as anticipated. In the first place, our criteria of cure by the last culture being sterile is often vitiated by the presence of a *Staph. albus* or diphtheroids which are for the most part probably contaminations. In

TABLE V. PYELITIS\* OF PREGNANCY. BACTERIOLOGIC STUDIES

Specimens cultured	228
Average per patient	8
Variation	2-16
<i>B. coli</i>	21 patients
<i>B. aerogenes</i>	4 patients
<i>B. coli</i> and <i>B. aerogenes</i>	1 patient
<i>Staph. aureus</i>	2 patients
<i>Streptococcus</i> (beta hem.)	1 patient
Some of the following organisms were present on one or more occasions in all but 5 cases	
<i>Strept. nonhemolytic</i>	19
<i>Staph. albus</i>	12
Diphtheroids	7
<i>B. aerogenes</i>	4
<i>B. coli</i>	2
<i>Chromobacterium</i>	2

\*See footnote Table IV.

TABLE VI. PYELITIS\* OF PREGNANCY. CORRELATION OF TYPE OF INFECTION AND DOSAGE TO RESULTS

ORGANISM		DOSAGE	DRUG "CURE"†	FINAL "CURE"‡	LAST CULTURE STERILE
<i>B. coli</i>	10	"Small" (2 gm. daily)	7	7	7
<i>B. aerogenes</i>	3	"Small" (2 gm. daily)	2	2	2
<i>B. coli</i> and <i>B. aerogenes</i>	1	"Small" (2 gm. daily)	0	1	1
<i>Strept. (hemolytic)</i>	1	"Small" (2 gm. daily)	0	0	0
<i>Staph. aureus</i>	1	"Small" (2 gm. daily)	1	1	1
<i>B. coli</i>	5	"Large" (over 4 gm. daily)	4	3	1
<i>Staph. aureus</i>	1	"Large" (over 4 gm. daily)	0	0	0
<i>B. coli</i>	6	"Large" + "Small"	0	5	3
<i>B. aerogenes</i>	1	"Large" + "Small"	1	1	1
Total	29		15 (52%)	20 (69%)	16 (55%)

\*See footnote Table IV.

††See footnotes, Table II.

TABLE VII. BACILLURIA\* IN GYNECOLOGY. CLINICAL DATA 18 PATIENTS

Type of Operation:	
Plastic repair	10
Laparotomy	1
Insertion of stem pessary	1
Nonoperative	6
Type of Infection:	
<i>B. coli</i>	12
<i>B. aerogenes</i>	5
<i>B. proteus</i>	1
Number of specimens cultured 83, average 4.6 per patient.	

\*Cystitis, chronic infection, urinary tract symptoms, or in a few cases prophylactic use of the drug.

"2 gm. daily" was employed the blood level of free sulfanilamide was usually 2 to 4 mg. per cent and the urine concentration about 40 to 75 mg. per cent. Where the "medium" dosage was used the figures were 5 to 7 mg. per cent in the blood and 100 to 150 mg. per cent in the urine. The concentrations in the blood with "large" dosage varied from 7 to 15 mg. per cent and in the urine from 200 to 400 mg. per cent. This information in addition to frequent bacteriologic studies of the urine are essential for the intelligent and successful treatment of patients with this disease.

TABLE II. BACILLURIA\* OF PREGNANCY.

## Results of Treatment

ORGANISM		DRUG CURE†	FINAL CURE‡	LAST CULTURE STERILE
<i>Ante partum</i>				
<i>B. coli</i>	10	10	9	4
<i>B. coli</i> + <i>B. aerogenes</i>	2	2	1	1
Strept. (nonhem.)	1	0	0	0
<i>Post partum</i>				
<i>B. coli</i>	32	28	24	12
<i>B. coli</i> + <i>B. aerogenes</i>	7	4	4	3
(hemolytic)	2	0	1	1
Strept. (nonhem.)	2	1	1	1
Staph. (albus)	1	1	1	1
Total	57	46 (81%)	41 (72%)	23 (40%)

\*See footnote Table I.

†Drug cure, causative organism disappeared from urine during therapy. It may, however, have reappeared in later specimens.

‡Final cure, causative organism not present in final specimens. (Usually 3 in number.) Streptococcus, staphylococcus, or diphtheroids may be present in either group.

TABLE III. BACILLURIA\* OF PREGNANCY. CORRELATION OF DOSAGE TO "CURE"

DOSAGE	COURSES	"DRUG" CURE†	"FINAL" CURE‡	LAST CULTURE STERILE
Small (1.5-2 gm. daily)	1	20	20	11
	2	9	8	5
	3	4	4	1
	4	1	1	1
Medium (2-4 gm. daily)	1	3	3	2
	3	1	0	0
Large (4-7 gm. daily)	1	6	5	3
	1 + S <sup>§</sup>	2	0	0
Total		46 (81%)	41 (72%)	23 (40%)

\*See footnote Table I.

††See footnotes, Table II.

TABLE IV. PYELITIS\* OF PREGNANCY. CLINICAL DATA

Mild: 8	Moderate: 13	Severe: 8
11 Bilateral		
7 Right		
11 Unknown (mostly right ?)		
15 Ante partum (onset 1-125 days before delivery)		
14 Post partum (onset 1-150 days after delivery)		
Febrile course 2-17 days. Temperature normal before starting drug in 7 cases. At least 6 had nitrogenous retention in blood.		
Follow-up studies averaged 4 months		

\*Includes pyeloureteritis and pyelonephritis.

many, although not all instances, the same may apply to cocci included in the nonhemolytic streptococcus group. When we have carried out quantitative tests, the total number of these organisms present has frequently been very small. If, however, these organisms appear repeatedly, they are, I believe, indicative of a low grade chronic infection. In such instances it is not uncommon for the *B. coli* to reappear in the urine at a later date, sometimes months after the sulfanilamide therapy. Accordingly, therefore, patients designated as having "final cure" as shown in the various tables, probably represent the best index of the favorable results. If our findings were calculated from the microscopic examination of stained urinary sediment, I am sure the cure rate would be very definitely increased. Again our failures sometimes occurred in patients with incomplete follow-up study and treatment.

We have not been able to duplicate the excellent results obtained by Kenny,<sup>2</sup> who advised relatively small dosage (1.5 to 1.8 gm. daily for five to seven days), by the use of either small or large dosage. Since Kenny's report, Cuthbert<sup>11</sup> has reported further experiences on urinary tract infections in the puerperium from the same hospital. He used a somewhat larger dosage, i.e., 2.25 to 3 gm. per day. His results are decidedly better than ours, but his follow-up observations are quite inadequate and accordingly vitiate his results to some extent. In the evaluation of results in obstetric and gynecologic urinary tract infections, the following fundamental considerations must be kept constantly in mind.

1. Gram-negative bacilli are foreign to the urinary tract of healthy gravid and nongravid women. Accordingly, our responsibility to the patient is not completed until we are assured that these organisms are not present in the urine.

2. The employment of cultural methods for the diagnosis of bacteria in the urine is far superior to reliance solely on the stained sediment.

3. Infection during pregnancy or the puerperium develops primarily because of anatomic and physiologic changes in the tract, because of congenital abnormalities, or because of trauma which is most frequently associated with labor and delivery. In gynecology these infections frequently occur as a result of anatomic or pathologic changes adjacent to the urinary tract or as a result of operative procedures.

4. The infecting organism is a gram-negative bacillus in over 90 per cent of the cases (106 out of 115 in the present study).

5. Bacilluria developing during pregnancy or the puerperium does not necessarily represent tissue invasion or actual infection. At the same time it is always the precursor of infection and accordingly infection frequently follows bacilluria.

6. Spontaneous disappearance of gram-negative bacilli from the urinary tract, when associated with infection, rarely ever occurs during pregnancy, but not infrequently happens after delivery.

7. The treatment of urinary tract infections "par excellence" is the immediate termination of pregnancy. Crabtree<sup>12</sup> has reported a spontaneous cure rate of 66 per cent by the fourth month post partum in a series of 44 patients with bacilluria. McLane<sup>22</sup> found in a group of

TABLE VIII. BACILLURIA\* IN GYNECOLOGY. DOSAGE OF SULFANILAMIDE AND RESULTS

ORGANISM		DOSAGE	DRUG CURE†	FINAL CURE†	LAST CULTURE STERILE
<i>B. coli</i>	9	Small (1.5-2 gm daily)	7	8	6
<i>B. coli</i>	2	Medium (2-4 gm. daily)	1	1	0
<i>B. coli</i>	1	Large (4-6 gm. daily)	1	1	0
<i>B. aerogenes</i>	5	Small (1.5-2 gm. daily)	1	1	0
<i>B. proteus</i>	1	Medium (2-4 gm. daily)	0	0	0
Total	18		10 (56%)	11 (61%)	6 (33%)

Four patients had other forms of therapy, bladder irrigations, etc. Follow-up incomplete in 8 cases

\*See footnote Table VII.

††See footnotes, Table II.

TABLE IX. PYELITIS IN GYNECOLOGY. CLINICAL DATA 11 PATIENTS

Mild: 5	Moderate: 5	Severe: 1
Febrile course 3 to 10 days, average 6 days		
Fever subsided before sulfanilamide therapy 1 patient		
Type of operation:		
Plastic repair		7
Laparotomy		3
Nonoperative		1
Type of infection:		
<i>B. coli</i>		9
<i>B. coli</i> and <i>B. aerogenes</i>		1
<i>B. aerogenes</i>		1
Number of specimens cultured 52, average 4.7 per patient		

TABLE X. PYELITIS IN GYNECOLOGY. DOSAGE OF SULFANILAMIDE AND RESULTS

ORGANISM		DOSAGE	DRUG CURE*	FINAL CURE*	LAST CULTURE STERILE
<i>B. coli</i>	3	Small 1.5-2 gm. daily	1	3	2
<i>B. coli</i>	2	Medium 2-4 gm. daily	0	0	0
<i>B. coli</i>	4	Large 4-6 gm. daily	2	3	2
<i>B. coli</i> and <i>B. aerogenes</i>	1	Medium 2-4 gm. daily	0	0	0
<i>B. aerogenes</i>	1	Large 4-6 gm. daily	1	1	1
Total	11		4 (36%)	7 (64%)	5 (45%)

Variation of sulfanilamide determinations (Urine 46-333 mg. %)

(Blood 4-16.1 mg. %)

Largest decrease in Hg during therapy—14%.

Drug fever in 2 patients.

\*See footnotes,†† Table II.

TABLE XI. SUMMARY. URINARY TRACT INFECTIONS

GROUP	NUMBER OF PATIENTS	DRUG CURE*	FINAL CURE*	LAST CULTURE STERILE
Obs. Bacilluria	57	46 (81%)	41 (72%)	23 (40%)
Obs. Pyelitis	29	15 (52%)	20 (69%)	16 (55%)
Gyn. Bacilluria	18	10 (56%)	11 (61%)	6 (33%)
Gyn. Pyelitis	11	4 (36%)	7 (64%)	5 (45%)
Total	115	75 (65%)	79 (69%)	50 (43%)

Total cultures studied 818

\*See footnotes,†† Table II.

The results of treatment in gonorrhea have been very dramatic. The discharge and other clinical symptoms disappear very promptly. Early in our study we treated three patients with relatively small dosage

TABLE XII. GONORRHEA. CLINICAL DATA

AGE	PATIENTS
15-20	10
21-25	8
26-30	5
31-35	6
36-40	5
Total	34
Race	
White	26 (76.5%)
Black	8 (23.5%)
Married	15
Single	14
Divorced	5

TABLE XIII. GONORRHEA. CLINICAL DATA

PREVIOUS PREGNANCIES	PATIENTS
0	18
1	11
2	3
4	2
4 treated during pregnancy	
1 treated during puerperium	
1 conceived and delivered since therapy.	
Acute initial infection	21
Exacerbation or reinfection	13
Lower genital tract infection	17
Lower and upper genital tract infection	17
Arthritis (elbow)	1
Fever, average duration 6 days (due to disease)	11

TABLE XIV. GONORRHEA. CLINICAL DATA

DURATION OF SYMPTOMS	PATIENTS
None	5
Less than 7 days	4
1-4 weeks	14
1-3 months	8
3-12 months	3
Interval between diagnosis and treatment	
0-7 days	24
8-24 days	7
35-80 days	3

TABLE XV. GONORRHEA. INITIAL BACTERIOLOGIC STUDY\*

Cervical cultures positive	31
Cervical smears positive	17
Cervical smears extracellular forms only	8
Urethral cultures positive	22
Urethral smears positive	8
Urethral smears extracellular forms only	3

\*32 patients where both culture and smear were taken before therapy.

71 ante-partum patients not treated with sulfanilamide, who had pyelitis, that *B. coli* was eliminated from the urine in 47 or 66 per cent in from eleven days to three years. One of the earliest spontaneous cures with which I am acquainted occurred in a patient of ours with a severe ante-partum pyelitis who had fever for twenty-four days prior to delivery. The urine culture revealed *B. coli* three days before delivery. She had negative cultures for *B. coli* from the bladder, right and left kidneys on the thirteenth day of the puerperium without any special therapy after delivery.

Bearing these facts in mind great caution must be exercised in drawing conclusions. We are, however, very much impressed with several observations. First, the longer the infection is present the more difficult is its eradication. Second, that sulfanilamide therapy *per se* may sterilize the urine but, in the presence of strictures or fibrosis of the ureter, the infection often returns after a course of treatment. Third, the use of intravenous pyelograms and cystoscopy for diagnostic purposes is essential, especially in instances where the infection fails to respond or a positive culture recurs after ceasing the medication. The number of cystoscopic examinations can, however, be greatly reduced. In the fourth place the elimination of *B. coli* in the ante-partum group, as shown in Table IV, is of fundamental importance. This is not a coincidence and suggests a most effective method of preventing the more serious urinary tract infections. The average duration of the febrile phase of the disease, in the 40 patients with pyelitis, was six days. The drug was not started until after the temperature returned to normal in 8 cases, while in the additional cases, especially during our early experience, it was not started until sometime after the onset of the febrile reaction. Traut<sup>27</sup> found a decrease of approximately 50 per cent in the length of the febrile reaction in sulfanilamide treated patients, as compared to a group that were not treated by this drug.

A study of all the "final cure" failures, 36 in number, suggests that 26 are largely due to inadequate dosage or incomplete follow-up. Another five were in-patients with long-standing urinary tract infections. Other unknown factors also must have played some role in these failures. Accordingly it appears that most urinary tract infections will respond to adequate sulfanilamide therapy. The earlier and milder the infection in question the better the response will be. Long-standing and severe infections usually necessitate larger dosage. In general if the patient does not respond to such therapy one should think of parenchymal involvement of the kidney, perirenal infection, or extraurinary tract disease.

#### GONORRHEA

Tables XII to XIX summarize the clinical and laboratory data relative to 34 patients who had gonorrhea. We are indebted to the New York Department of Health for referring many of these patients to us for treatment.

(1.5 to 3.6 gm. daily) for five to seven days per course. The rapid subsidence of the clinical symptoms was very encouraging; however, cultures and sometimes smears continued to be positive. This suggests a possible danger in that patients receiving as much as 20 gm. of sulfanilamide during one week in an ambulatory state may show marked clinical improvement and even negative smears, yet they are possible serious sources of infection. Bomze<sup>23</sup> has recently reported his experience treating 45 ambulatory patients with approximately 2.6 gm. per day in courses of five days' duration. This makes about 13 gm. per course. He reports only one failure, but 14 recurrences, which he attributes to reinfection. In view of our early but limited experience with ambulatory patients, and the fact that his study apparently is based on smears without cultures it would seem possible that he may be erroneous in attributing all his recurrences to reinfection.

Following our early experience, it became evident that considerably larger dosage was necessary. Since that time, all patients treated have been hospitalized and kept in bed during their entire treatment. Under these conditions the drug is tolerated much better, toxic symptoms are detected as they appear, and laboratory facilities can be utilized to the fullest extent. In addition to these advantages under this system of treatment, we have not had a single instance of an extension of the infection from the lower to the upper genital tract. It was previously noted that nine of the 34 patients developed drug fever. This and the previously cited reasons make me feel very strongly that this disease in the female should not be treated by sulfanilamide in ambulatory patients.

It appears to be unusual to diagnose and treat women during the early days of the disease. Only four of our patients gave a history of symptoms of less than seven days' duration. Another five cases gave no symptoms, being discovered by contact studies, but probably had, more or less, long-standing infections. Accordingly, the important observation, made by many authorities treating male patients, that the acute cases do not respond as favorably as the chronic infections, probably is not of great importance in the treatment of this disease in the female.

This study very clearly demonstrates the superiority of cultural methods over smears for the diagnosis and control of treatment in gonorrhea. Occasionally, the smears will be positive for extracellular forms only and the cultures negative, however, the reverse is very much more often the case. Carpenter and others<sup>19</sup> in a recent statistical analysis of diagnostic methods found the cultural method 191 per cent superior to the smear method.

The dosage varied from 4.2 to 6 gm. daily, an average of 4.9 gm. This was calculated on a basis of 1 gm. of the drug to each 20 to 25 pounds of body weight. The duration of treatment varied from five to eleven days, but in most cases the drug was prescribed over seven consecutive days. No other form of treatment was prescribed. Cure of the lower genital tract infection by repeated cultures and smears was established in all patients before discharge. Two single delinquent

TABLE XVI. GONORRHEA. CONTROL BACTERIOLOGIC STUDIES

Positive cultures	88
Negative cultures	457
Unsatisfactory cultures	2
Total	547
Average per patient	16
Positive smears	45
Extracellular forms only	28
Negative smears	455
Total	528
Average per patient	15.5
Total Specimens Studied	1075

TABLE XVII. GONORRHEA. SULFANILAMIDE TREATMENT\*

Approx. average daily dose	4.9 gm.
Approx. average duration of therapy	7.3 days
Approx. average total dose	36.9 gm.
3 patients received 2 of above courses of therapy	
2 for exacerbation or reinfection	
1 Pelvic inflammatory disease with masses for evaluation	
Cure—negative cultures and smears established in all cases. Two patients readmitted 15-30 days after discharge with exacerbation or reinfection.	

\*All patients hospitalized 8 to 34 days (av. 13.8 days). (3 patients treated prior to admission, daily dose 1.5-3.6 gm. for 7 days. Total dosage average 20 gm. All failures.)

TABLE XVIII. GONORRHEA. FOLLOW-UP

1-16 months. Average per patient 3.06 mo.	
Inadequate follow-up, i.e., less than 2 months, 7 patients	
Average cultures and smears per patient 16	
<i>Toxic Symptoms</i>	
None	12 patients
Headache	15 patients
Cyanosis	11 patients
Dizziness	11 patients
Nausea	11 patients
Fever	9 patients
Vomiting	3 patients
Anorexia	3 patients
Rash	2 patients
Palpitation	1 patients
Note: Several patients received nicotinic acid to relieve symptoms or prophylactically.	

TABLE XIX. GONORRHEA. BLOOD OBSERVATIONS

	PATIENTS
W.B.C. count over 10,000 on admission	18
Lowest W.B.C. count recorded 6,000	
W.B.C. count increased during therapy in	7
W.B.C. count over 10,000 on discharge in	9
Highest W.B.C. count on discharge 12,600	
Hemoglobin per cent decreased in	20 (58%)
Hemoglobin per cent decreased more than 10% in	8 (24%)
Hemoglobin per cent decreased more than 20% in	2 (6%)
Largest decrease in hemoglobin 28%	
Blood sulfanilamide over 10 mg. % in 8 patients (24%). Only one patient failed to reach a blood concentration of 5 mg. %.	



this country, with this disease, are women. As this incidence is greater than that of any other communicable disease, the responsibility of the gynecologist and obstetrician is obvious.

I am convinced from my experience in treating patients with gonorrhea that:

1. The original diagnostic procedure and all follow-up examinations should include cultures as well as smears.

2. Adequate dosage (5 to 6 gm. daily) for about seven days is necessary for the successful treatment of the disease.

3. Cure is effected during the first forty-eight hours of therapy in the majority of patients, but occasionally it takes at least five days.

4. Gradually decreasing dosage of the drug is not indicated following the initial "high" dosage.

5. Hospitalization is essential for the satisfactory and safe employment of sulfanilamide.

6. Haphazard treatment with inadequate dosage often renders the patient asymptomatic. Such individuals may be a serious menace to society by spreading the disease, in addition to bringing discredit to this form of therapy.

#### PUERPERAL INFECTION

It was on this subject that Colebrook published his first observations in the *Lancet* of June 6, 1936. This was unquestionably of great importance in stimulating interest in the English-speaking world in these compounds. It is unfortunate that many of the subsequent contributions, by other authors, have failed to include accurate bacteriologic diagnoses and accordingly add but little to our knowledge. Our experience, it is true, is small, being limited to 20 cases. In a considerable number of these patients the drug was employed under carefully controlled conditions in order to evaluate results in the presence of different infecting organisms. However, our experience has been somewhat broader than is indicated in the puerperal infection group, because two-thirds of the patients reported with post-partum bacilluria had a febrile puerperium, and obviously in many cases the febrile reaction was due to genital tract infection. Cultures were obtained from the lochia in these patients. Tables XX and XXI summarize the results.

Definite therapeutic effects were obtained only on those patients with hemolytic streptococcus infections. Two of the 8 patients in this group

TABLE XX. PUERPERAL AND POSTABORTAL INFECTION. CLINICAL DATA

20 patients with moderate to severe infection. Fever 3 to 35 days. Average duration 11 days		
16 puerperal infection		
4 postabortal infection		
PATIENTS	BLOOD CULTURE POS.	INFECTING ORGANISM (UTERINE CULTURE)
8	2	Hemolytic strept. (beta)
8	2	Anaerobic nonhem. strept.
1	1	<i>Strept. viridans</i> .
2	0	Aerobic nonhem. strept.
1	0	<i>B. coli</i> and <i>B. aerogenes</i>

irresponsible colored girls in the second decade of life, one of whom was pregnant, were found to have negative cultures and smears at the time of their first follow-up examination after discharge, but both were positive when they returned for their second examination. One gave a history of repeated exposures during the interval, while the other denied such experiences. Both have been readmitted and re-treated and again their cultures and smears became negative and have remained so to date. Whether these two cases, represent an exacerbation of the original infection or a reinfection, I cannot say. In any event the other 32 patients have shown no evidence of recurrence or reinfection.

The dramatic results obtained can be realized when on analysis, we found that in 26 patients no positive culture or smear was obtained after starting treatment. In the remaining 8 patients, the laboratory diagnosis became negative in from one to five days and only 2 patients were in the five-day group. As previously stated smears and cultures were usually taken at two-day intervals during hospitalization. In a very recently treated patient not included in the present series where specimens were examined every four hours, the urethral culture was found to be negative in eleven hours and the cervix in twenty-four hours after the institution of treatment. Rare pleomorphic extracellular forms were occasionally found in the cervical smear for the following two days.

It has not been our experience that sizable thick-walled pelvic masses were in any way affected by the sulfanilamide therapy. This is contrary to the experience of J. H. Long, as quoted by Long and Bliss<sup>16</sup> and Grodberg and Carey<sup>20</sup> and others who found a decrease in size, resolution, or disappearance of the masses. However, acute or subacute salpingitis of specific origin, not complicated by secondary infection, has in our experience responded well to the drug. Recently, in several patients with sizable pelvic masses, we have employed "nonspecific" fever therapy after completion of the sulfanilamide treatment. No conclusions can as yet be drawn from these few patients.

If we count the two above mentioned cases as failures, which seems dubious, our cure rate by the criteria employed is 94 per cent. Figures in the literature vary from about 30 to 95 per cent. However, there is great variation in daily dosage and total duration of treatment. In 312 female patients reported by four different authors the average cure rate was 65 per cent. As many of the patients in this composite series were controlled only by smear the results cannot be regarded as being entirely reliable. Mahoney<sup>24</sup> has recently reported a comparable series to the here reported cases. The patients were all hospitalized, he employed large dosage, and they were all controlled by both smear and culture. It is interesting to note that according to his criteria 93.4 per cent were cured.

The results then are very superior, if the patients are properly treated, to any of the older forms of therapy such as, the application of local antiseptic substances, local heat, nonspecific protein injections, serums, vaccines or specific fever therapy. It appears probable that about one-fourth of the million patients who are infected annually in

statements: It is usually indicated in hemolytic streptococcus infections especially if the patient is ill. I say "usually," advisedly, because most hemolytic streptococcus infections during the puerperium are local in extent and recovery, without any serious sequelae, occurred in about 95 per cent of cases before the advent of these new drugs. Present-day knowledge, it is true, implies that many of these infections were probably caused by organisms belonging to groups other than Group A (Lancefield). If there is an associated septicemia, peritonitis, or other evidence of spread of the infection, the drug should be started early, the dosage should be high and determinations of the concentration of the drug in the blood made frequently. In such cases a concentration of at least 10 mg. per cent should be maintained. Repeated blood cultures serve as an excellent guide during the critical period of illness. In anaerobic and aerobic nonhemolytic streptococcus infections, there is no evidence that the drug will in any way alter the clinical course of the disease. There is no evidence of which I am aware, to show that the drug affects infections in the genital tract with organisms of the colon aerogenes group. Recently, Sadusk<sup>17</sup> following the work of Bohlman<sup>18</sup> has reported the successful treatment of a *B. welchii* infection in two cases of postabortal infection with positive blood cultures. Serious infections with this organism although infrequent have always in the past produced a high mortality. Accordingly, if possible, they should be diagnosed early and treated with large dosage when encountered. Other supportive forms of therapy including transfusions should be used as well as the sulfanilamide in our therapy.

The pneumonia group of patients are shown only to complete the picture. In general, the results are most dramatic. In such a serious complication, we are reluctant to rely entirely on sulfapyridine if an antisera is available for the type of pneumococcus isolated. Early diagnosis and prompt treatment are essential to good results. I have summarized in Table XXII the pertinent data in relation to seven patients, all of whom recovered, who have been treated with sulfapyridine. It is interesting to note that on our obstetric service we have had an average of one death per year from pneumonia during the years 1932 to 1937, inclusive, while no deaths have occurred during the past two years. Such information is of course not statistically significant.

In the miscellaneous group it is gratifying to note the improvement in the patient with lymphogranuloma venereum. The dosage employed was relatively low (1.8 gm. daily) over a rather long period of time (twenty-two days) somewhat as suggested by Shropshear, whose results are quite stimulating. It is interesting to note that the blood stream became sterile following treatment, in the patient with the overwhelming hemolytic streptococcus infection. This patient subsequently died primarily because of the infection, although she did have a chorionepithelioma with early lung metastases. Table XXIII presents the pertinent data.

TABLE XXI. PUERPERAL AND POSTABORTAL INFECTIONS.  
TREATMENT (SULFANILAMIDE)—RESULTS

PATIENTS	DAILY DOSE	TOTAL DOSE
2	1.5 gm.	13.5-15 gm.
18	4-6 gm.	20-45 gm.
Clinical course modified by drug in,		
2* Hemolytic streptococcus infections		
1 Anaerobic streptococcus infection (also urinary tract infection)		
1 Anaerobic streptococcus infection (? effect)		
1 <i>Strept. viridans</i> infection (discharged with pelvic mass)		

\*The hemolytic streptococcus disappeared from the vaginal secretions in from five to twenty-three days in the six other cases.

had positive blood cultures but they were not severely ill patients. In fact all 8 patients may have recovered without sulfanilamide. There was suggestive evidence of response in 3 other cases but, as Table XXI shows, the findings are not clear-cut. I have yet to see conclusive evidence of a favorable response in puerperal infection where the infection is due to organisms other than the hemolytic streptococcus. Colebrook,<sup>13</sup> although his reported clinical experience with other types of puerperal infection is small, is of the same opinion. In a recent report by Morris,<sup>14</sup> we are not informed of the bacteriologic findings, and despite the fact that he has treated 97 cases of puerperal and postabortal infection with more than an equal number of controls, his findings are of no value, to my mind, in drawing conclusions, other than the broad statement that there is little response to this form of treatment in post-partum or puerperal infection in general. It is of the utmost value as far as the welfare of the patient is concerned to have accurate information concerning the nature of the infecting organisms. I must completely disapprove of Long's<sup>15</sup> advice in his recent monograph, namely, "that the chances of a given puerperal infection being hemolytic streptococcal in origin are overwhelming, and hence, sulfanilamide should always be prescribed at the first sign of the disease." Long<sup>15</sup> has wrongly drawn his conclusions as to incidence of the hemolytic streptococcus in puerperal infection from the work of Colebrook and Purdie<sup>13</sup> who were reporting primarily only on hemolytic streptococcus infections treated with sulfanilamide. Quite naturally then, the latter authorities reported 100 instances of hemolytic streptococcus infection and an additional 6 cases, 3 of whom were staphylococcus infections and the other 3 anaerobic streptococcus infections. In the latter group there was no definite therapeutic effect noted. As I have previously pointed out, the incidence of beta hemolytic streptococcus infections is so low in proportion to those caused by other organisms which, as far as we know, are for the most part not affected by the drug, that to give all patients with puerperal infection sulfanilamide would be in direct contrast to the best interests of the patient. Bacteriologic investigation of the nature of the infection, if not already under way should certainly be started coincident with "the first sign of the disease."

To summarize our information concerning the indications for the use of sulfanilamide in puerperal infection, we may make the following

5. The primary infecting organism was eliminated from the urinary tract in 69 per cent of a group of 115 obstetric and gynecologic patients with bacilluria or pyelitis, who were treated with sulfanilamide.

#### *Gonorrhea.*—

6. Employing relatively high dosage of sulfanilamide in hospitalized patients, for a relatively short period of time, gonorrhea in the female can probably be cured by the criteria of repeated cultures and smears in a large percentage of cases. The cure rate was at least 94 per cent in the 34 patients here reported.

7. For the successful and safe employment of sulfanilamide in the present state of our knowledge we are not justified in treating the disease by this means in ambulatory patients.

8. Cultures are essential for accurate diagnosis and are a much more reliable index of cure, than smears alone. However, the best results are obtained when both cultures and smears are employed.

#### *Puerperal and Postabortal Infections.*—

9. Prophylactic cultures should be taken where later infection appears probable.

10. Sulfanilamide is usually indicated in infections caused by hemolytic streptococci or *B. welchii*.

11. The drug is not known to exert any definite therapeutic effect in other types of infection.

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#### DISCUSSION

DR. REUBEN OTTENBERG—(By invitation).—In the genitourinary cases that I have had the opportunity to follow, the commonest cause of failure has been obstruction. If there is any remaining mechanical obstruction in the urinary tract, such as stone stricture, it will prevent a cure, or give a temporary apparent cure. Shortly after the drug is stopped, the same micro-organism will be found still infecting the tissues.

TABLE XXII. PNEUMONIA—(SULFAPYRIDINE)

STATUS	ORGANISM	DOSAGE	RESULT
1 Antepartum	Pneum. Type I	33.0 gm. + serum	Dramatic response
1 Postpartum	Pneum. Type I	44.0 gm. + serum	Dramatic response
1 Antepartum	Pneum. Type XVIII	22.5 gm.	Dramatic response
1 Postoperative	Pneum. Type I	19.0 gm.	Excellent response
1 Postoperative*	Pneum. Type III	67.0 gm.	Fair response
1 Antepartum	Pneum. not isolated	33.0 gm.	Excellent response
1 Postpartum	Pneum. not isolated	14.7 gm.	No response

\*Developed nonhemolytic streptococcus blood stream infection from local operative site during high dosage of sulfapyridine. Sulfanilamide later with no effect.

TABLE XXIII. MISCELLANEOUS

DIAGNOSIS	DRUG	RESULT
1 Pelvic peritonitis followed Rubin's Test and Coagulation of cervix	Sulfanilamide 5 days (total dosage 21.6 gm.)	No response
1 lymphogranuloma venereum	Sulfanilamide 22 days (total dosage 40 gm.)	Remarkable improvement (also had local applications)
1 chorionepithelioma (admitted 2 months post partum)	Prontosil and prontosil 7 days (1936) "adequate" dosage.	1. Blood culture 500 col. per c.c. 2. Blood culture 30 col. per c.c. 3. Blood culture 15 col. per c.c. 4. Blood culture no growth Died 9 days after admission
1 subacute bacterial endocarditis	Sulfanilamide 10 days (total dosage 32.4 gm.)	Blood culture <i>Strept. viridans</i> No response

## CONCLUSIONS

*General.*—

1. Bacteriologic examinations of urine, blood, lochia, cervical and urethral secretions, etc., are of the greatest importance in the diagnosis, control and evaluation of chemotherapy in infections in obstetrics and gynecology.

*Urinary Tract Infections.*—

2. Organisms of the colon aerogenes group are the chief cause of urinary tract infections, complicating obstetric and gynecologic conditions. The urine under such circumstances can usually be rendered sterile with varying amounts of sulfanilamide. Subsequent follow-up is necessary because re-infection may recur if the same conditions subsequently exist as were present prior to the initial infection.

3. The urinary tract should be free from organisms before the patient is finally discharged. It is usually more difficult to render the urine sterile where the infection has been severe or has existed over a long period of time.

4. In ante-partum bacilluria and definite pyelitis, the urine was rendered bacilli-free and kept so in 10 of 13 cases. This fact is of great importance in the prevention of pyelitis. The earlier the diagnosis and treatment, the better the results will be.

that time. It was a case which the initial diagnosis was streptococcus pneumonia because hemolytic streptococci were obtained from the sputum at the time of admission, and not pneumococci. Therefore, the patient was put on sulfanilamide for one day: on the second day pneumococci were found, serum was given and sulfanilamide was discontinued. The patient ran the usual course, and the pneumonia got better. But two weeks later when the patient was ready to be discharged from the hospital, he developed acute agranulocytosis with total disappearance of leucocytes from the blood and was dead in less than three days. In this case then there was a free interval. Apparently the moderate dosage of the drug for twenty-four hours only produced this result. Therefore, I do not think it is necessary to have prolonged, heavy dosage of the drug to produce agranulocytosis. It is the unexplained idiosyncrasy of the patient. The need for care in the use of the drug is obvious, but I am afraid that even constant watching of the leucocytes is of relatively little value in the prevention of agranulocytosis.

Four of the 5 patients with agranulocytosis that I have seen died. The patient that survived recovered after profuse transfusion therapy.

The complication, agranulocytosis may occur with either sulfanilamide or sulfapyridine. It is undoubtedly rare but perhaps not so rare as the published cases would lead one to think, for I keep hearing of unpublished cases.

The last complication is a new one and occurs only with sulfapyridine. It is the complication of hematuria due to a precipitate of acetylated sulfapyridine in the urinary tract. I have seen only two of those cases, one of them not a very severe hematuria, which subsided on the liberal administration of fluids. The other patient was a young man with acute bronchopneumonia, who was on sulfapyridine in the usual dosage. On the third day he developed an intense hematuria and in about forty-eight hours there was complete suppression of urine. In spite of every effort to get the kidneys to secrete again, it was impossible to do so and he died of uremia. A postmortem examination was done and amorphous deposits were found in the ureter and pelvis of the kidneys and in the tubules of the pyramids of the kidneys. Death was due therefore to mechanical obstruction. The only way we have to prevent such a condition is the liberal administration of fluids with the drug.

On account of these possible toxic effects I agree with the attitude of Dr. Douglas that these drugs must be used only in proved infections with micro-organisms that are potentially of serious import, that they must be used with great care, and that the patient, particularly in the first few days of treatment, must be under close daily supervision by his physician.

DR. ALBERT H. ALDRIDGE.—It is obvious that the most satisfactory results of treatment are likely if the types of bacteria causing the infections under treatment are known; if the twenty-four hour dose of the therapeutic agents to be used are determined according to body weight; if uniform concentrations of the drugs in the blood stream are maintained by regular four hourly administration of proper amounts of fluid as well as of the drugs being used and finally if the concentrations of the drugs in the blood stream are checked by one of the tests devised for the purpose.

In attempting to avoid the toxic effects of these new therapeutic agents, clinicians have probably often used doses too small to be effective. The results of careful pharmacologic and clinical studies such as those that have been presented will help to establish essential facts regarding effective doses, the seriousness of the toxic manifestations and the relative therapeutic value of these chemical agents as compared to former methods of treatment.

The value of sulfanilamide in the treatment of post-partum infections has been emphasized. In large series of patients with post-partum streptococcal infection treated at Queen Charlotte, Lane Roberts has reported a reduction in mortality from 22.5 to 5.3 per cent since sulfanilamide has been used. Sulfapyridine has become a valuable means of treating respiratory infections which occur after operation and in connection with pregnancy. Women who go into labor while suffering from acute respiratory infections not infrequently present serious problems for treatment in the post-partum period.

I wish to stress particularly the clinical toxicity of the drug. I do not refer to the minor effects, such as skin eruptions, cyanosis, the slight mental disturbance, dullness, and confusion that sometimes occur and which are not of serious import. I refer particularly to the grave, possibly fatal toxic results which must be classed as idiosyncrasies, which occur in human beings and not in animal experiments. No one knows how frequent they are; they probably do not add up to over 2 or 3 per cent of all cases. I am going to discuss particularly four serious complications: (1) acute hemolytic anemia; (2) jaundice; (3) agranulocytosis; and (4) urinary obstruction from sulfapyradine.

In the Johns Hopkins experience, as cited in the recent book of Long and Bliss, acute hemolytic anemia occurs in from 2 to 4 per cent of the cases. The condition is rarely fatal, although there have been two or three fatal cases reported in the literature. I have seen five typical severe cases, all of whom got well although two nearly died. Acute hemolytic anemia invariably occurs in the first three or four days of treatment, which has a very important bearing on the way that treatment should be started and watched by the physician. Most commonly there is a free period, i.e., one or two days of relative well-being between the onset of drug treatment and the appearance of symptoms. The two most severe cases that I have seen received the drug in small doses for one day only. In one instance the patient had 4 or 5 gm. of sulfanilamide in one day; the other received the same plus 20 c.c. of prontosil intramuscularly. There was a free interval of two days in both cases; on the third day they were suddenly markedly anemic, and vomited a material resembling coffee grounds. They also had diarrhea with coffee-ground appearance, intense hemoglobinuria, high fever, and mild jaundice. These two patients both developed marked oliguria, and one had suppression of urine for something over twenty-four hours. Both had marked retention of nitrogen in the blood. The therapy consisted of blood transfusion and large amounts of fluid parenterally.

The next complication I wish to discuss is jaundice, which is closely related to anemia. Jaundice usually occurs with acute hemolytic anemia, but there is a considerable number of cases in which jaundice occurs without it. When carefully studied by the usual method of liver function tests, those patients show unmistakable evidence of liver damage. I have seen seven such cases, but only three of them were very severe and only one of them died. That patient undoubtedly had acute yellow atrophy of the liver, although unfortunately no autopsy was obtained. This patient was a young man who was given sulfanilamide for mastoiditis, in the usual dosage. He developed a not very severe acute hemolytic anemia and the drug was stopped. The mastoiditis continued and he was given the drug again for a week. This was a mistake, because the drug should never be given again if the patient has developed acute hemolytic anemia (unless he has some probably fatal infection such as meningitis). There was a free interval of a week following this, after which he developed what looked like a mild jaundice. It got steadily worse and at the end of a month he died with all the symptoms of acute yellow atrophy of the liver.

Another patient with severe jaundice had apparently partially recovered. He was seen by me five months later and at that time he was still slightly jaundiced and had an enlarged spleen. He undoubtedly had developed chronic nodular sclerosis of the liver which, as you know, sometimes occurs after acute hepatic degeneration and which ultimately is likely to be fatal.

The third complication is agranulocytosis. I am not referring now to mild or moderate depression of the leucocyte count which probably never has any relation to acute agranulocytosis at all. The cases of agranulocytosis have not had this moderate depression, but instead the disappearance of granulocytes occurred suddenly, the leucocyte count previously having been over 5,000 per c. mm. and with the usual number of granulocytes. I have seen 5 cases of agranulocytosis, 4 of them fatal.

Agranulocytosis, unlike acute hemolytic anemia, does not occur in the beginning of therapy but only ten days or two weeks after. In most instances it occurs when very heavy dosage has been used over ten days or two weeks, although one patient that I saw received the drug for only one day, 6 gm. being given during



heart disease, and pyelitis. Second were those labors which were associated with more than one probable cause, totaling 102 labors and were in the main combinations of the major single causes, and finally a series of miscellaneous single causes of varying incidence and importance amounting to 60 labors.

Of the major single causes of prematurity eclamptogenic toxemia was seen most frequently. This complication was recognized when the blood pressure read 140/90 or over. The presence of albumin, a weight gain of five pounds or more in two weeks, stubborn edema, headaches, spots before the eyes, and dizziness were often additional signs. Twenty-five per cent of the premature labors having a probable single etiology were associated with this condition.

Premature detachment of the placenta was present in 38 instances. These cases did not always give the classical picture of premature separation. Lesser degrees of detachment were usually exhibited. Pain was not a common early symptom but bleeding was always present. Examination of the placenta following delivery revealed a portion sufficiently detached to produce premature labor. The term premature separation of a low lying placenta is more appropriate.

The presence of syphilis and multiple pregnancy followed in close order with 36 and 32 cases, respectively. The low incidence of syphilis as a probable cause of prematurity in our clinic may be explained by the fact that routine Wassermann and Kahn tests are done at the first prenatal visit and if found positive, antisyphilitic therapy is begun at once. A history of habitual abortion was present 15 times. Placenta previa was associated with prematurity in 14 cases. Nephritic toxemia was present in 13 labors. There were 10 instances of heart disease, while pyelitis was seen in combination with premature birth on only 6 occasions (Table I).

TABLE I. PROBABLE MAJOR SINGLE CAUSES OF PREMATUREITY  
(Total Probable Known Causes 434)

	LABORS	PER CENT
Eclamptogenic toxemia	108	24.9
Premature detachment of placenta	38	8.7
Syphilis	36	8.3
Multiple pregnancy	32	7.3
Habitual abortion	15	3.4
Nephritic toxemia	13	2.9
Heart disease	10	2.3
Pyelitis	6	1.4
Total	272	

In the 102 labors which were related to two or more probable causes of prematurity, habitual abortion and eclamptogenic toxemia were found grouped together in 15 instances. Habitual abortion was recognized when the patient had previously aborted twice. Multiple pregnancy and eclamptogenic toxemia were in combination 11 times. Premature detachment of the placenta and syphilis were found in relation to eclamptogenic toxemia in 7 and 6 cases, respectively. One is impressed with the frequency of combined causes of prematurity and with the importance of eclamptogenic toxemia. In addition to the 108 labors in which it was the single pathology involved, toxemia was present in 43 instances where combined etiology was a factor.

Sixty labors were related to single miscellaneous causes of prematurity. The chief condition in this group were those operative procedures which were done because of maternal and fetal distress alone without apparent underlying obstetric pathology at the time. The operations included forceps delivery, bag induction of labor, and version with extraction.

Of the 819 premature infants, 216 died. There were 114 infants which were born alive yet died in two weeks, and 102 were stillborn for a gross mortality of 26.3 per cent. The 819 premature infants were analyzed in weight groups. Sixty were found to weigh between 400 and 1,000 gm. Seventy-one infants weighed between 1,000 and 1,500 gm., while 170 premature infants ranged from 1,500

DR. RICHARD CHARLTON.—Dr. Douglas mentioned fever as a complication in the course of chemotherapy. In a case at the Lawrence Hospital, after eight days of 6 gm. daily doses of sulfanilamide given to control postabortal sepsis, the temperature reached 108.6° F. The drug was discontinued, and in forty-eight hours the temperature returned to normal. At the time when the elevation reached 108.6° F. the pulse rate was 200.

Dr. Marshall has made an important observation relating to possible deleterious effects of sulfanilamide on the fetus in utero. At the Lawrence Hospital, in the presence of infection late in pregnancy, we look upon sulfanilamide as contraindicated.

DR. EDWARD G. WATERS.—During 1937 and 1938 we had 19,830 deliveries with a morbidity from pelvic sepsis in 464 cases. Of that number, 50 patients were treated with sulfanilamide. Eleven patients had repeated positive blood cultures. Nine of these eleven were due to hemolytic streptococcus, one was due to the *B. coli*, and one to the *Streptococcus viridans*. Of this group of 11 patients we had two deaths, one of which was caused by the hemolytic streptococcus, and the other by the *Streptococcus viridans*.

Although 11 cases with a positive blood stream infection in a group of 53 patients with puerperal morbidity is a small series, nevertheless the results seem to me to be significant.

Dr. Douglas is to be commended for reiterating that with sulfanilamide treatment one should insure the patient against toxic complications by following the blood sulfanilamide level and carrying out a constant check on the white blood cell count, hemoglobin readings, etc.

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## OBSTETRIC FACTORS IN PREMATURE BIRTH\*

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THE premature infant has been defined as an infant which weighs not less than 400 gm. nor more than 2,500 gm., measures in length not less than 28 cm. nor more than 48 cm., and is not less than twenty-two weeks in gestation nor more than thirty-seven weeks.

At the Research and Educational Hospitals of the University of Illinois College of Medicine, Department of Obstetrics and Gynecology, Chicago, from May 1, 1925, to March 1, 1939, there were 10,797 labors with subsequent childbirth in the In-patient and Out-patient Services. Of this number 765 labors were apparently premature. There were 50 twin births and two triplet births. A total of 819 premature infants therefore resulted from the 765 premature labors. There were 401 male infants born and 418 females.

A probable cause of prematurity was found in 434 labors. Of the probable causes three groups were recognized.

First in importance were those major single causes which accounted for 272 labors, namely, eclamptogenic toxemia, premature detachment of the placenta, syphilis, multiple pregnancy, habitual abortion, placenta previa, nephritic toxemia,

\*Abridgment of Thesis submitted to the Faculty of the Graduate School of Medicine of the University of Pennsylvania in partial fulfillment of the requirements for the degree of Master of Medical Science (M.Sc. (Med.)) for graduate work in gynecology-obstetrics.

tions were done because of probable obstetric causes of prematurity also discussed above. There were 31 deaths for a mortality of 32.9 per cent.

In 37 cesarean sections 8 fetal deaths occurred. The use of forceps on 14 occasions was related to 3 deaths, while version with extraction was associated with 4 deaths in 11 births. Eight deaths resulted from 21 attempts at bag induction of labor. The high mortality attending operative manipulations to deliver a premature infant should cause the operator to be more cautious (Table III).

TABLE III. ABNORMAL PRESENTATIONS AND POSITIONS ASSOCIATED WITH MORTALITY OF PREMATURE INFANTS

	NO.	DEATHS
Breech	92	40
Occiput posterior	41	8
Face	7	2
Shoulder and hand	4	3
Total	144	53
Group mortality 36.8 per cent		

Although the mortality of the premature infant as a whole in this study was 26.3 per cent, those infants weighing 1,500 gm. or over had a comparatively low mortality of 14.1 per cent. This low figure may be attributed partly to the fact that no barbiturates are used as analgesia in our clinic. One-fourth grain of morphine sulphate is given to the patient for rest if delivery is not expected within three hours. This is repeated when necessary. At the time of delivery, drop ether is administered as the head passes over the perineum. A left lateral episiotomy is used following thorough infiltration of the perineum with 1 per cent novocaine.

Prematurity associated with maternal age groups revealed the greatest number of premature labors in women between the ages of 20 and 25 years. There were 262 or about one-third of the total. Next in significance was the age group from 15 to 20 years, which reached 164 labors. In the period from 25 to 30 years 156 premature labors occurred. There was a gradual decline thereafter to reach a low of one premature labor in the age group of 45 to 50 years. Six labors occurred in patients from 10 to 15 years, and of these five were in colored girls.

Possible seasonal influence upon premature labor was analyzed. It was found that the greatest number of labors appeared in May, next in prominence was July and August and then December and January. Activities about the house and garden in spring were thought to influence the high incidence of premature labors in May. Increased summer temperatures possibly encouraged prematurity in July and August, while the exciting holiday season of December and January may have played an important role at that period. Recourse to the calendar as an explanation of an undetermined etiology might be of value.

Management of prematurity from an obstetric standpoint should begin with prophylactic measures. Since eclamptogenic toxemia, syphilis, premature separation of the placenta, habitual abortion, and multiple pregnancy play the most important roles as probable causes of prematurity, therapy should be directed toward control of those conditions.

Eclamptogenic toxemia which accounted for 25 per cent of the single probable causes of prematurity in our series offers a problem. Early recognition in prenatal examinations and the institution of bed rest, milk diet, and one ounce of magnesium sulphate daily will go far in keeping this condition under control. Many premature labors occurred, however, with the management of toxemia in progress. Early diagnosis of the toxemia type of patient followed by measures for its control would be a direct way of combating prematurity arising from this source.

Colvin and Bartholomew<sup>1</sup> have drawn our attention to the increased incidence of hypothyroidism early in pregnancy of those patients who have a tendency toward eclamptogenic toxemia. With this hypothyroidism there is a corresponding hypercholesteremia. If routine basal metabolic rates and cholesterol de-

to 2,000 gm. The largest group from 2,000 to 2,500 gm. totaled 518 infants. Of the 400 to 1,000 gm. group only 4 premature infants survived a two weeks' postnatal period. Many of these infants were nonviable premature infants. That is, they fell between the figures twenty-two to twenty-eight weeks in gestation and 28 to 35 cm. in length. In the 1,000 to 1,500 gm. group 13 lived. There was a marked drop in mortality when the infants weighed from 1,500 to 2,000 gm. There were 114 premature infants who survived. The best results were secured in the 2,000 to 2,500 gm. group where 472 lived (Table II).

TABLE II. ANALYSIS OF MORTALITY IN EACH WEIGHT GROUP

(Total Premature Infants 819)

WEIGHT GROUP	NO.	PER CENT MORTALITY
400-1,000 gm. (60)		93.3
Born alive and survived	4	
Born alive and died	36	
Stillbirths	20	
1,000-1,500 gm. (71)		81.7
Born alive and survived	13	
Born alive and died	35	
Stillbirths	23	
1,500-2,000 gm. (170)		32.9
Born alive and survived	114	
Born alive and died	24	
Stillbirths	32	
2,000-2,500 gm. (518)		9.1
Born alive and survived	472	
Born alive and died	19	
Stillbirths	27	
Gross mortality 26.3 per cent		

The highest infant mortality was found in relation to syphilis. In 36 premature births there were 18 deaths. Six of these infants weighed from 400 to 1,000 gm. Of infants born of mothers having a history of habitual abortion, there were 6 deaths in 15 births. Three deaths occurred in the group weighing from 400 to 1,000 gm. Of 13 infants delivered from nephritic patients, there were 5 deaths. Three of these fatalities came in the 1,500 to 2,000 gm. group. In 11 births, necessitating operative deliveries because of fetal or maternal distress not related to probable major causes of prematurity, there were 4 deaths. One death occurred in each of the 4 weight groups. Premature detachment of the placenta was found associated with 13 deaths and 38 births. There were 3 deaths each in the 1,000 to 1,500 gm. and 2,000 to 2,500 gm. weight groups. Eclampsogenic toxemia was related to 25 deaths in 108 births. In the 1,000 to 1,500 gm. and 2,000 to 2,500 gm. weight group, there were 8 deaths each. Placenta previa had 3 deaths in 14 births. Two occurred in the group weighing from 1,500 to 2,000 gm. The conclusion may be drawn that the probable causes of prematurity in our series were concurrently leading obstetric factors in premature infant death.

The association of abnormal presentations and positions with prematurity and death revealed a mortality of 36.8 per cent.

Breech presentation was present in 92 instances for an incidence of 11.2 per cent or approximately four times its normal incidence. Since breech presentation is relatively common during the last trimester of pregnancy, an increased occurrence would be expected with prematurity. There were 40 deaths related to breech delivery for a mortality of 43.4 per cent. The danger of breech delivery in the premature infant is not generally appreciated. In this study it was approximately twice that of those infants presenting by the vertex. Persistent occiput posterior was present in 41 cases. There were 8 deaths. There were 7 births with a face presenting and four with a shoulder and hand.

Operative procedures were used to effect delivery of the premature infant in 94 instances. With the exception of 11 cases previously mentioned those opera

Following birth, active therapy should continue during the immediate postnatal period under the supervision of an obstetrician in consultation with a pediatrician. The obstetrician should be responsible by reason of his presence at the delivery and because of his training to interpret possible obstetric causes of prematurity.

The premature infant may be overtreated as well as undertreated. Adequate heat and oxygen and frequent small feedings of mother's breast milk diluted with water are of major importance. Most premature infants take feedings through the medicine dropper well. The use of gavage is valuable. The gavage form of feeding, however, in the very young premature infant carries a great deal of shock from trauma and may defeat its purpose. To combat dehydration and to meet the infant's water requirements subcutaneous fluids are invaluable. Two ounces of 5 per cent dextrose and saline solution may be used twice daily.

In our clinic, whole blood is used in the jaundiced infant and in those infants where cerebral hemorrhage is present or suspected. Early attention to gastrointestinal upsets, upper respiratory symptoms and to cutaneous disturbances will go far in aborting a fatal diarrhea, a pneumonia, or an impetigo.

#### DISCUSSION

Comparable premature studies have been infrequent. Various authors have dealt with the subject of etiology, mortality, and treatment of prematurity from different angles. Clifford<sup>5</sup> in 1934, Breese<sup>6</sup> in 1938, Waddell<sup>7</sup> in 1937, Ingram<sup>8</sup> in 1937, Dunham<sup>9</sup> in 1936, Hirst<sup>10</sup> in 1939 and Swanson<sup>11</sup> in 1936 made valuable additions. Our study of the premature infant was conducted primarily from the viewpoint of the obstetrician.

Of the 765 premature labors a probable cause of prematurity could be accounted for in only 434 instances. This deficiency should encourage a concentrated attempt to determine the cause of premature delivery in all instances. Of the 216 premature deaths, 143 were associated with probable causes of prematurity. Autopsy reports were misleading. There were cases of atelectasis, slight cerebral hemorrhage, or minor lacerations of the tentorium which did not explain the cause of death. Many reports were returned with negative findings.

As a corollary to every obstetric service there should be, therefore, a committee upon whom rests the obligation of determining the cause of premature labor and birth. Coincident with this objective each premature death should have a careful investigation. This should include an autopsy study done by one skilled in the interpretation of premature infant pathology. By combining these goals successfully, the etiology and management of prematurity will be simplified and premature death will be explained upon a more rational basis.

#### SUMMARY

1. Of 10,797 labors with subsequent births at the Research and Educational Hospitals of the University of Illinois, 765 labors were premature. There were 52 multiple pregnancies which produced a total of 819 premature infants.

2. The probable causes of prematurity were chiefly eclamptogenic toxemia, premature detachment of the placenta, syphilis, multiple pregnancy, habitual abortion, placenta previa, nephritic toxemia, heart disease, and pyelitis.

terminations were made on all pregnant women at or about the fourth month, it might be possible to reduce the incidence of toxemia by the administration of Lugol's solution to those patients having a hypothyroidism or hypercholesteremia.

Syphilis has long been recognized as a prominent cause of prematurity. The early and adequate onset of antisyphilitic therapy would reduce this factor to a minimum. If treatment is begun before the fifth month of pregnancy, prematurity rarely occurs.

Multiple pregnancy as an important cause of prematurity stimulates early contractions of the uterus. This may be due to increased intrauterine tension or to the presence of one or more abnormal fetal positions or because of premature rupture of membranes. Premature detachment of a normally implanted or a low lying placenta will also encourage uterine contractions. These contractions stimulate further detachment and premature labor ensues. Placenta previa may be a cause of prematurity by the same reasoning applied to premature separation of the placenta. In fact, it may be extremely difficult to distinguish clinically between a low lying placental detachment and a marginal placenta previa. In the management of those conditions associated with premature uterine contractions, some form of therapy to allay uterine irritability would be in form.

TABLE IV. OPERATIVE PROCEDURES ASSOCIATED WITH MORTALITY OF PREMATURE INFANTS

	NO.	DEATHS
Cesarean section	37	8
Bag induction	21	8
Forceps	14	3
Version and extraction	11	4
Vaginal hysterotomy	3	3
Artificial rupture of membranes	4	1
Dührssen's incisions	2	2
Craniotomy	1	1
Cervical polypectomy	1	1
Total	94	31
Group mortality 32.9 per cent		

In 1936 Falls<sup>2</sup> drew attention to the advantage of using progestin to control uterine contractions in the treatment of threatened and habitual abortion. Since then because of the expense of the drug, he has adopted the use of an aqueous solution of corpus luteum extract as a means to control those conditions. Continuing his investigations, Falls has advanced the influence of corpus luteum therapy to include placenta previa, premature detachment of the placenta, premature rupture of membranes, and premature labor proper. The results which he has attained are most encouraging.<sup>3</sup>

For the patient who habitually aborts, one rabbit unit is used twice weekly early in pregnancy before the onset of symptoms. If threatened abortion occurs, one rabbit unit is used twice daily. The latter dose applies also to premature rupture of membranes, premature labor, premature separation of the placenta and placenta previa. Dosage is reduced relative to the response secured.

Management of the premature infant to reduce the operative mortality rate offers many difficulties. The younger the premature infant the less are its chances for living. In our series those infants weighing under 1,500 gm. had a mortality of 87.0 per cent. Early episiotomy and low forceps when the head is on the perineum may be used to reduce the length of the second stage. However, unindicated and unintelligent use of operative procedures may predispose the premature infant to extensive cerebral damage with possible death or insanity.<sup>4</sup> This is of particular significance in the management of the premature breech. Attempts at breaking up an extended breech should be few. Efforts to depress the aftercoming head into the pelvis are to be criticized. Extreme gentleness is absolutely necessary.

## TYPES OF PLACENTA PREVIA AND METHOD OF DELIVERY

In 324 cases the type of placenta previa was noted. The marginal type occurred in 158 cases, the partial in 83 cases, and the central in 83 cases. Vaginal deliveries were employed in 74 (46.8 per cent) marginal, 26 (31.8 per cent) partial, and 17 (20.5 per cent) central placenta previa. Cesarean section was the method of delivery in 85 (53.2 per cent) marginal, 57 (68.2 per cent) partial, and 66 (79.5 per cent) central placenta previa. The total number of vaginal deliveries were 122 as compared to 209 cesarean sections.

## CESAREAN SECTION AND PARITY

In the 209 cesarean sections performed, 28.8 per cent were in primigravidas and 71.8 per cent were in multigravidas. In the primigravidas delivered by cesarean section, 53.3 per cent were of the marginal type; 28.3 per cent, partial; and 18.4 per cent central. In the multiparas, 34.4 per cent were of the marginal type; 29.0 per cent, partial; and 36.6 per cent central placenta previa.

## CONDITION OF THE CERVIX

In 272 cases the condition of the cervix was noted. In the vaginal delivery group, the cervix was closed in only 5 cases; the cervix was dilated between 1 and 2 cm. in 18 cases; between 3 and 4 cm. in 30 cases; and between 5 cm. and full dilatation in 38 cases. In the cesarean group, the cervix was closed in 98 cases; was dilated from 1 to 5 cm. in 83 cases; and in no case was the cervix dilated over 5 cm.

## BLOOD TRANSFUSION

Since 1927 we have been employing blood transfusion with greater frequency. Thus in 195 cesarean deliveries blood was given in 27.7 per cent of the cases, while in 72 vaginal deliveries it was used in 17.57 per cent of the cases. Blood is made available for every case and is given whenever needed.

## MATERNAL MORTALITY

In Tables I and II are tabulated the maternal mortality according to the method of delivery and the cause of death. It is important to note that the principal cause of death in the vaginal group is hemorrhage and in the section group it is infection. The total gross mortality was 3.62 per cent; 6.6 per cent for the vaginal deliveries, and 1.9 per cent for the cesarean section group.

TABLE I. METHOD OF DELIVERY AND MATERNAL MORTALITY

METHOD OF DELIVERY	NUMBER	MATERNAL DEATHS
Total deliveries	331	12 (3.62%)
Dilatation of cervix, internal podalic version and breech extraction	55	7
Amniotomy and spontaneous	15	0
Amniotomy and Willett clamp	4	0
Forceps	9	1
Breech extraction	8	0
Podalic version	1	0
Spontaneous	30	0
Total vaginal deliveries	122	8 (6.6%)
Classical	172	3
Low cervical	36	1
Porro	1	0
Total cesarean sections	209	4 (1.9%)

## MATERNAL MORBIDITY

The maternal morbidity is three times as great in the abdominal deliveries as compared with the vaginal deliveries, 63 and 22 per cent, respectively. How-

3. There were 216 premature deaths. Probable causes of prematurity were present with premature death in 143 instances.

4. The gross infant mortality was 26.3 per cent. Infants under 1,500 gm. had an 87.0 per cent mortality, while those 1,500 gm. and over had a mortality of 14.1 per cent.

5. A thorough understanding of obstetric complications is of prime importance to manage adequately premature labor. An aqueous solution of corpus luteum extract to control premature uterine contractions is an important adjunct in the management of prematurity.

6. Skilled autopsy examination by one familiar with premature infant pathology is necessary to determine the cause of death.

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1819 WEST POLK STREET

## A STUDY OF RESULTS IN 332 CONSECUTIVE CASES OF PLACENTA PREVIA

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THE following constitutes an analysis of 332 cases of placenta previa treated at the University Hospital from 1920 to 1938, inclusive, and at the Baltimore City Hospital from 1935 to 1938, inclusive. Since both hospitals employ the same method of treating placenta previa, and since both obstetric departments are headed by the same chief of service, together with a similarly trained attending and house staff, it is logical that these cases be grouped together.

#### AGE AND RACE

In the age group up to 29 years, there were 198 cases; from 30 to 39 years there were 113 cases; and from 40 years on, there were only 21 cases. This condition occurred in 214 white and in 117 negro patients. We have noted this preponderance of patients in a previous report but are unable to offer any explanation in view of the fact that we have a greater negro clinic population.

#### PARITY AND DURATION OF PREGNANCY

Placenta previa was found to occur in 71 (21.4 per cent) primigravidas and in 261 (68.6 per cent) multigravidas. Sixty-eight per cent of the cases occurred between the thirty-fourth week of gestation and term, thus indicating a high percentage of viable babies.



## DISCUSSION

From this study we are impressed with the importance of an early diagnosis of placenta previa employing every safe method of diagnosis, bearing in mind the need to prevent hemorrhage, to conserve and replace blood.

In the last few years we have carried out the following routine in the handling of all cases of suspected placenta previa. Every patient who has painless bleeding is immediately hospitalized. Her blood is promptly matched, grouped, and a donor secured. If a compatible donor is not available, or if the patient is bleeding seriously, we immediately secure blood from our "Blood Bank." If time permits and the patient is in good condition, a soft tissue technique x-ray is taken to visualize the placenta. If a vaginal examination is necessary to make the diagnosis as to type of previa and condition of the cervix, the operating room is set up; the operating team is ready and prepared to immediately perform a cesarean section; and all materials necessary for a vaginal delivery are on hand. Then and only then is a vaginal examination done.

The method of delivery has a definite relationship to maternal mortality. In every case the method of delivery should be individualized, depending upon the type of placenta previa, the amount of hemorrhage, the condition of the cervix, as well as the question of vaginal infection. Nevertheless, manual dilatation of the cervix with internal podalic version is to be condemned. If vaginal delivery is to be done, the most important thing to bear in mind is to control hemorrhage and then only to complete the delivery after the cervix normally becomes fully dilated. Thus rupture of the membranes with or without the use of the Willett clamp has given satisfactory results in selected cases in controlling hemorrhage, while the cervix is dilating. The same is true in bipolar version where the buttocks are used as a tamponade until the patient is ready for delivery. We almost never employ in our clinic the hydrostatic bag, for it is felt that it is less safe both from the standpoint of infection and that of hemorrhage. In the employment of cesarean section in placenta previa, we are influenced first by the type of placenta previa and second by the condition of the cervix. Thus in central and partial placenta previa we favor cesarean section. In marginal types, if the cervix is long and undilated, we likewise will perform a section, reserving the vaginal route for the dilated cervix, especially in the multipara. This is demonstrated by the fact that in the primigravida 53.3 per cent of the sections were of the marginal type as compared with 34.3 per cent in the multigravida. We have employed the low cervical section with satisfactory results.

The maternal mortality, from the point of view of the type of delivery, favors the abdominal section. This is well demonstrated by the fact that over a period of eighteen years, with more careful selection of cases for vaginal delivery, we have been unable to reduce our maternal mortality, while in the same period of time with the employment of the cesarean section, we have definitely and gratifyingly reduced it.

TABLE II. CAUSES OF MATERNAL DEATHS IN 332 CASES OF PLACENTA PREVIA

VAGINAL DELIVERIES (122)	MATERNAL DEATHS
Causes of Deaths:	
Ruptured uterus	1
Hemorrhage and shock	6
Hemorrhage—not delivered	(1)
Septicemia and peritonitis	1
Total number	8
Percentage	6.6%
CESAREAN DELIVERIES (209)	MATERNAL DEATHS
Causes of Deaths:	
Hemorrhage and shock	1
Peritonitis	1
Generalized peritonitis and paralytic ileus	1
Hemorrhage and bronchopneumonia	1
Total number	4
Percentage	1.91%

ever, in the great number of cases the condition was very mild, just falling within the morbidity standard.

## FETAL MORTALITY

The fetal mortality was 60 (48.8 per cent) and 58 (27.8 per cent) in the vaginal and section cases, respectively. While it is obvious that the fetal mortality is reduced in the section deliveries, it is more important to know what percentage of viable babies are saved in the two groups and in each type of previa. In Table III we give these figures.

TABLE III. FETAL MORTALITY. SURVIVAL OF VIABLE\* BABIES AFTER DELIVERY BY VAGINA VERSUS CESAREAN SECTION

	DELIVERY BY VAGINA			DELIVERY BY CESAREAN SECTION		
	MAR-GINAL	PARTIAL	CENTRAL	MAR-GINAL	PARTIAL	CENTRAL
No. of deliveries	75	25	17	86	57	66
No. of babies	75	25	17	86	57	66
Nonviable babies	8	2	2	0	0	3
Viable* babies	67	23	15	86	57	63
Stillbirths	19	11	7	2	1	14
Neonatal deaths	8	4	2	14	10	16
Survived	40	8	6	70	46	36
Percentage of survived viable babies	59.7	34.8	40.0	81.4	80.7	57.1
Percentage of survival all types by vaginal route:				51.42 per cent		
Percentage of survival all types by cesarean route:				73.8 per cent		

\*Babies weighing over 1,500 gm. and/or over twenty-eight weeks' duration.

## FETAL ABNORMALITIES

We were unable to find any record of fetal abnormalities in the vaginal deliveries, but there were 5 cases in the section series. The relationship of monstrosities and congenital anomalies to placenta previa is of interest. Murphy believes that there is no greater incidence of this finding in placenta previa than over the general incidence in all cases, while Greenhill in a very exhaustive study of the literature finds that there seems to be a relationship between the two conditions.

# Y A STUDY OF 111 CYSTOGRAMS FOR DIAGNOSIS OF PLACENTA PREVIA\*

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THE purpose of this paper is to present a comprehensive study of the use of the cystogram in the diagnosis of placenta previa and to point out certain failures of the method. The work was first undertaken about May, 1937. A preliminary report covering 19 cases was prepared by me in collaboration with Dr. John A. McGeary and read before the Section on Obstetrics, at the New York Academy of Medicine, Nov. 23, 1937. The present report includes those cases and others collected during the intervening period up to October, 1938. During this time a total of 111 cystograms were done on 105 patients in the third trimester of pregnancy.

Until 1934 various methods<sup>7</sup> were used in conjunction with the x-ray for the diagnosis of placenta previa. Since all of these methods involved the injection of foreign materials directly or indirectly into the uterine cavity, they entailed the dangers of intrauterine infection, premature rupture of the membranes, premature induction of labor, fetal death in utero, intrauterine hemorrhage, or perforation of maternal (occasionally fetal) viscera. Snow and Powell<sup>8</sup> in 1934 wrote that with careful study one could locate the placental site in the ordinary anteroposterior or lateral films of the abdomen. Other authors pointed out that calcifications in the mature placenta could be visualized in the usual films of the abdomen.

In the same year Ude, Weum, and Urner<sup>12</sup> suggested the use of the cystogram, and in 1935 Ude and Urner<sup>9, 10</sup> reported its use in 35 cases of third trimester bleeding.

In the present series the technique of Ude and Urner has been followed. There were 105 patients upon whom 111 cystograms were done. The discrepancy is accounted for by repetition on those few cases which were admitted to the hospital more than once during the same pregnancy, or who were kept under observation for longer than usual. For the purposes of this paper the cases are divided into three groups:

1. Patients proved not to have had placenta previa at the time of parturition.
2. Patients in whom placenta previa was demonstrated at the time of delivery.
3. Patients with presentations other than vertex.

## RESULTS

There were 78 patients in whom placenta previa was not found when they delivered. Of these, 17 were controls without a history of bleeding, and the remainder were patients who gave a history of third trimester bleeding. There were 83 cystograms done on these 78 patients. In none of the 17 controls was an x-ray diagnosis of placenta previa made, and in none of them was it dem-

\*Read at a meeting of the Broome County Medical Society, Oct. 10, 1939.

Findley, after an analysis of 47,828 cases of placenta previa collected from world-wide literature states, "The incidence of cesarean section has increased from 6.07 per cent to 15.29 per cent during the past fifteen years while the maternal mortality rate has been more than halved and falls way below the group delivered from below." The importance of liberal blood transfusions and the great help of having blood available at all times in the form of a "Blood Bank" is life saving in many instances.

From the point of view of the baby, it is well-recognized that the best chances for life of the baby is by abdominal delivery. In this study we are struck by two considerations: first, the greatest number of cases is beyond the thirty-second week of pregnancy; and second, the survival of viable babies is greatly increased by cesarean section in all types of placenta previa. For these reasons, without increasing the risk of the mother by cesarean section in properly selected cases, we should give the baby its best chance for survival.

#### SUMMARY AND CONCLUSIONS

1. The results of 332 consecutive cases of placenta previa are presented.
2. The more frequent and liberal use of blood transfusions is paramount in reducing maternal mortality and morbidity.
3. The method of delivery must be determined for each individual case, depending upon the type of placenta previa and the condition of the cervix.
4. Accouchement forcé, internal version and breech extraction are condemned in the treatment of this condition.
5. The rupture of membranes with or without the use of the Willett clamp will give favorable results in the properly selected cases.
6. The employment of cesarean section definitely reduces the maternal and fetal mortality in the central and partial types of placenta previa and in certain selected cases of marginal placenta previa.
7. The maternal mortality in this series is 6.6 per cent in vaginal deliveries and 1.9 per cent in cesarean section.
8. Deaths in viable babies are greatly reduced by the employment of cesarean section.

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giving rise to a false positive interpretation of the film. Subsequent review of the cystograms in the above cases showed gas and feces present in all. This may be the explanation in these cases, but rectal contents are visible in most of the negative plates also. Obviously the upward displacement of the head depends on the quantity of the rectal content.



Fig. 2.—Case 15. M. R., 39 years old, primigravida, with vaginal spotting three or four days, at 8 months' gestation. Cystogram shows space between vertex and bladder of 4.4 cm. in midline and 4.5 cm. on right, 3.5 cm. on left. Cesarean section two weeks later, placenta implanted posteriorly except for anterior one-third which covered cervix and lower segment on anterior wall to level of vesicouterine peritoneal reflection.

In the eighth patient mentioned above, at operation the bladder was found situated high on the lower uterine segment, adherent to the upper portion of a previous low vertical incision. This circumstance may well be analogous to one mentioned by Ude, Urner, and Robbins<sup>11</sup> in which there was a nonoperative upward displacement of the bladder, giving rise to a false positive cystogram.

There were 19 patients in this series in whom placenta previa was found. Nineteen cystograms were done, placenta previa was correctly prognosticated in 13,

onstrated at delivery. However, in the remaining 61 patients, of a total of 66 cystograms done, 10 showed x-ray evidence pointing toward placenta previa which was not substantiated at the time of parturition.

Every patient in this series was examined vaginally at the time of delivery to determine the site of implantation of the placenta. Nine patients came to cesarean section for other causes; 14 patients showed evidence of a partial premature separation of the placenta at delivery. In none of the latter was there any abnormal space between the head and the bladder which might have been caused by blood clots as mentioned by Ude and Urner.<sup>9, 10</sup>



Fig. 1.—Case 13. A. R., multipara, with painless vaginal bleeding at seven and one-half months. Cystogram shows greatest distance between head and bladder 0.4 cm. Vaginal examination showed edge of placenta to right and posterior, with 2 fingers' dilatation of the cervix.

There were 8 patients in whom a false diagnosis of placenta previa was offered on the evidence of the cystogram. Seven of these patients were delivered vaginally and showed no placenta previa. One of these 7 demonstrated a partial premature separation of the placenta, which was situated high in the fundus. There were no clots in front of the head which might have caused the increased vesicocephalic space. The eighth patient was delivered by cesarean because of cephalopelvic disproportion; no previa was found.

It seems rather obvious from the foregoing cases that false positive reports may occur. The explanation is difficult to deduce. All of these cases had been done before publication of a paper by Ude, Urner, and Robbins<sup>11</sup> came to our attention. They urged administration of low colonic flushes before x-ray, feeling that distention of the rectum with feces and gas has frequently caused upward displacement of the head,

There were 9 cystograms taken on 8 patients with the breech presenting. In one case the first cystogram showed the breech 3.5 cm. above the bladder; the second cystogram twelve days later showed the breech sitting on the bladder shadow. Of the 9 cystograms, 2 were useless because of poor delineation, 22.22 per cent; placenta previa was incorrectly diagnosed in three, 33.33 per cent; incorrectly ruled out in two, 22.22 per cent; and correctly ruled out in two, 22.22 per cent. With such a marked variability, even though only a few breeches are considered, the cystogram seems of questionable value here.

In the whole series of 111 cystograms (see Tables I and II), the diagnosis by x-ray was correct in 88 instances (79.28 per cent), incorrect

TABLE I

Group 1: No placenta previa at delivery	
Controls	17
Bleeding cases	61
Total cystograms	83
X-ray diagnosis correct	73 (87.95%)
X-ray diagnosis incorrect	10 (12.05%)
Group 2: Placenta previa found at delivery	
Cases	19
Cystograms	19
X-ray diagnosis correct	13 (68.42%)
X-ray diagnosis incorrect	6 (31.58%)
Group 3: Presentations other than vertex	
Cases	8
Cystograms	9
X-ray diagnosis correct	2 (22.22%)
X-ray diagnosis incorrect	5 (55.55%)
X-rays useless	2 (22.22%)

TABLE II

Summary of series	
Cases	105
Cystograms	111
Placenta previa correctly diagnosed	13 (11.71%)
Placenta previa correctly ruled out	75 (67.57%)
Placenta previa incorrectly diagnosed	13 (11.71%)
Placenta previa incorrectly ruled out	8 (7.21%)
Useless plates	2 (1.80%)
Total correct diagnoses	88 (79.28%)
Series with breeches eliminated	
Cases	97
Cystograms	102
Placenta previa correctly diagnosed	13 (12.75%)
Placenta previa correctly ruled out	73 (71.57%)
Placenta previa incorrectly diagnosed	10 (9.80%)
Placenta previa incorrectly ruled out	6 (5.88%)
Total correct diagnoses	86 (84.32%)

in 21 instances (18.92 per cent), and there were two useless plates (1.80 per cent). If the breeches are eliminated from the study, we have a total of 102 potentially useful cystograms; the x-ray diagnosis was correct in 86 instances (84.32 per cent), incorrect in 16 instances

68.42 per cent. It was incorrectly ruled out in 6 cases, or 31.58 per cent. Four patients came to cesarean section for placenta previa. The remainder were delivered vaginally and the diagnosis so checked. In one case there was a prolapsed arm in front of the head which caused a characteristic indentation in the placental shadow over the bladder.

In all six cases where placenta previa was incorrectly ruled out by the cystogram, the placenta was found implanted on the posterior wall of the lower segment, with varying portions of the placenta overhanging the cervical os (Fig. 1). Four patients had a partial placenta previa, two had marginal previa. In one patient (F. L.), Cystogram 7972 showed the head impinging on the bladder, while vaginal examination demonstrated the cervix  $2\frac{1}{2}$  fingers dilated with the placenta implanted directly on the posterior wall, covering about three-fourths of the os.

By contrast the following case of posterior implantation is detailed: M. R., a 39-year-old, white, para 0, gravida i, admitted because of vaginal spotting for three or four days. Uterus the size of an eight months' gestation, fetus small, head high. Cystogram 8246 showed a space between the vertex and bladder of 4.4 cm. in the midline and on the right, and 3.0 cm. on the left (Fig. 2). A probable diagnosis of placenta previa centralis was offered. Two weeks later with onset of further bleeding, cesarean section was done, and the placenta was found implanted on the posterior wall, except for the anterior one-third which covered the cervix and the lower segment on the anterior wall to the level of the vesicouterine peritoneal reflection.

It is interesting to note that in all of the cases where placenta previa was incorrectly ruled out by the cystogram the placenta was found implanted on the posterior wall, with only the margin, or one or two cotyledons overhanging the os. Furthermore it is logical that such an implantation should not displace the head upward sufficiently to give the characteristic cystogram. The placenta must be between the head and bladder in order to show such a relationship. Unless enough of a posteriorly implanted placenta extends over the os and upward on the anterior uterine wall sufficiently to widen the space between the head and the bladder, the interpretation will be negative. This is illustrated by the six cases mentioned above as contrasted with the case of M. R. where such a situation existed.

Until November, 1937, when a preliminary report of this work was read, the literature was void of any mention of the posteriorly implanted placenta previa, perhaps because such an implantation was considered marginal and of little danger. In the present series the classification of marginal, partial, and central previa has been based on a theoretical full dilatation of the cervix. Thus a marginal in relation to a closed cervix or with one fingerbreadth dilatation becomes a partial previa in relation to a fully dilated cervix. It has been our experience that the posteriorly implanted previa has all the dangerous potentialities of the anterior or lateral implantation. In the preliminary report mentioned above there was included one case of posterior placenta previa, and at that time we pointed out the impossibility of cystogram diagnosis in such circumstances. Since that time (until October, 1938), only one report, that of Jablonski and Meisels,<sup>4</sup> mentions that a posteriorly situated placenta previa may be overlooked. From a personal communication with Dr. Alfred C. Beek in May, 1938, I learned that in two of Beek's cases where the cystogram had failed to diagnose placenta previa, it had been found implanted posteriorly.



## CONCLUSIONS

1. The cystogram is useful in the diagnosis of placenta previa, but should always be correlated with the clinical findings.

2. A false positive diagnosis may be caused by upward displacement of the fetal head due to rectal distention. This can be corrected by rectal flushes in certain cases.

3. A placenta previa which is implanted on the posterior wall of the lower uterine segment with no portion thereof intervening between the fetal head and the bladder cannot be diagnosed by indirect placentography.

4. No patient with a history of third trimester bleeding should be discharged without a careful vaginal examination under proper precautions.

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## GÄRTNER'S DUCT LESIONS OF THE CERVIX

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GÄRTNER'S duct represents the persisting distal segment of the Wolffian or mesonephric duct. Its presence in the adult female is a phylogenetic anomaly. The cranial end of the Wolffian duct, however, is generally retained and unites with the proximal collecting tubules of the primitive kidney to form the epoophoron. This embryonal structure is normally encountered in the mesovarium and the lateral third of the mesosalpinx. The line of demarcation between the proximal and distal segments of the mesonephric duct has been shown by Robert Meyer to lie at a point between the caudal pole of the ovary and the wall of the uterovaginal canal. This has been demonstrated in a human embryo 30 mm. in length. With formation of the uterus and vagina, Gärtner's duct proceeds inferiorly between the layers of

(15.68 per cent). These figures may be compared with those of Beck and Light<sup>1</sup> who eliminated from their study the cases in which the vertex was not presenting. In their 71 cases of third trimester bleeding, diagnosis was correct in 63 (88.73 per cent), and incorrect in 8 (11.27 per cent). Whereas Beck and Light found placenta previa correctly diagnosed in 13 of 17 cases (76.47 per cent), and its absence correctly diagnosed in 50 of 54 cases (92.59 per cent); in the present series placenta previa was correctly diagnosed in 13 of 19 cases (68.42 per cent), and its absence correctly diagnosed in 73 of 83 cystograms taken on 79 cases (87.95 per cent).

#### DISCUSSION AND SUMMARY

The cystogram has been found useful as an aid in the diagnosis of placenta previa, but like all other laboratory tests, the findings must be weighed together with the clinical facts. It has been our practice to examine vaginally every case of third trimester bleeding on the ward service regardless of the x-ray report. In those cases where the report was negative, examination was made for corroboration and to ferret out the cause of the bleeding. In cases where x-ray offered a provisional diagnosis of placenta previa, examination was conducted in the operating room with a blood donor available. Where a positive diagnosis was offered and the patient had ceased bleeding, she was observed at bed rest in order to carry the child to a period of greater viability. If, however, bleeding recurred she was examined as above.

In cases where placenta previa is falsely postulated by the cystogram, no harm has been done. The upward displacement of the head may frequently be due to a distended rectum and sigmoid. The use of the colonic flush as advocated by Ude, Urner, and Robbins<sup>11</sup> before indirect placentography must of course depend upon the circumstances of the case. Needless to say, one is not going to give rectal treatment to a patient who is actively bleeding. Since the female rectum is almost always occupied by varying amounts of feces and gas, and since a false positive report was offered in only 9.80 per cent of 102 cystograms, we feel that the rectal flush may well be reserved for the patient who ceases bleeding. No patient should be discharged until she has been examined vaginally under aseptic precautions to determine the cause of the bleeding.

If all patients are subjected to such examination the posterior implantations, where a false negative report has been given, will be discovered and catastrophe at home avoided. An attempt was made by us to utilize the lateral plate to diagnose the posterior implantations. This was a failure in general although a small number were postulated. A review of a considerable number of laterals taken during routine pelvic stereoroentgenography showed no constant variation in the distance of the fetal head from the promontory of the sacrum in the seventh, eighth, or ninth month of gestation. Perhaps the development of a greater familiarity with the methods of Snow and others in the delineation of the placenta by soft tissue technique will help to solve this problem.

sterilization. The cervical cone which was radically amputated measured 25 mm. in length, 20 mm. transversely at the external os, and 20 mm. transversely at the apex. Both lips presented marked erosion of the papillary type. The endocervical mucosa was congested and its markings were prominent. The segment of muscle was fibrotic. The microscopic examination confirmed these gross observations. The posterior lip in addition showed remnants of Gärtner's duct, its radiating branches, and glands. The main canal proceeded downwards in a plane parallel to the long axis of the cervix and lay close to the endocervical mucosa (Fig. 1). Though relatively uniform it widened slightly as it continued inferiorly. Terminal branches proceeding obliquely from the main duct extended into the fibromuscular layer of the cervix to divide into gland clusters which occupied interstices between the muscle fibers. At the upper and lower extremities intraductal papillary formation was observed (Fig. 2). The lining epithelium of the main duct and its larger terminals varied from the cuboidal to



Fig. 1.— $\times 80$ . Gärtner's duct is noted to the left. One of its larger branches and the terminal glands are shown well in the fibromuscular coat of the cervix. The solitary layer of low columnar or cuboidal cells is distinctive. The cytoplasm is scant and pale, and the vesicular nucleus almost completely fills the cell body.

the flat type. The cells were small and with poorly defined cell membranes. The scant pale cytoplasm was filled by a round or oval vesicular nucleus, with a fine chromatin net work. The glands about the terminals were varied. Some were round, others oval, convoluted or papillary in contour (Fig. 3). The solitary layer of lining cells was somewhat taller than in the ducts. The cell membrane was focally recognizable. The morphology otherwise was similar. Secretion occasionally encountered was homogeneous and markedly acidophilic. About the main duct was a thin layer of loose, edematous cellular stroma. The glands, however, as previously observed were scattered between normal muscle and connective tissue fibers of the cervix.

The second specimen of cervix with normal Gärtner's duct rests was obtained after hysterectomy from Mrs. L. Z., aged 44 years (No. 31,801), admitted to the Long Island College Hospital, Feb. 4, 1937, complaining of intermittent lower abdominal pain and progressive menorrhagia. An abdominal tumor, solid in type, originated from the pelvis and extended practically to the ensiform process.

the broad ligament and not uncommonly enters the outer wall of the uterus. In Japanese women, J. Sakuraoka, found rests especially frequent in the corpus uteri, generally at the level of the round ligament and in the isthmus at the level of the internal os. Rests in the supravaginal cervix and portio, which are sites of predilection in the European female, were noted with less frequency. Leaving the uterus at the cervicovaginal junction, the duct further descends in the lateral wall of the vagina to reach the hymenal edge. The course of the duct, however, in both uterus and vaginal wall is extremely varied.

Persistence of Gärtner's duct in toto is rare. J. Sakuraoka records such a case in a 53-year-old woman. Small segments of the duct, however, are found in about 20 per cent of all adult females. The left side is apparently favored. The incidence increases after the age of seventeen, largely the result of growth of the duct which renders its recognition easier. Rests in the supravaginal cervix are most frequent, especially at the level of the internal os where the duct enters from the broad ligament and proceeds medially and inferiorly to lie close to the endocervix. Continuing into the vaginal section of the cervix, it turns laterally to reach the outer aspect of the portio where it generally terminates.

When observed microscopically, the morphology of the duct is distinctive. It presents as a simple tube which gradually widens as it proceeds inferiorly, and in the upper portion of the vaginal cervix produces an ampulla which is comparable to that of the vas deferens in the male. As it further descends the ampulla divides into branches which terminate in gland clusters. The branches are spiral, of small caliber, and generally proceed from the anterior and posterior aspects of the widening duct. They are concentrically arranged in relation to the inner surface of the cervix. The lumen of the main duct presents a distinctive lining of low cuboidal or flat epithelium. The cytoplasm is scant and clear. A small round or oval vesicular nucleus almost completely fills the cell body. The glands which originate by sacculation are generally round or oval and of small dimension. The lining epithelial cells are also cuboidal or low columnar with a poorly defined cell membrane. The cytoplasm is pale, and here too a round vesicular nucleus almost completely fills the cell body. The lumina not uncommonly contain secretion.

In a series of 1413 cervixes examined in the Gynecology Laboratory of the Long Island College of Medicine, between the years of 1923 and 1938, only one contained normal remnants of Gärtner's duct. The explanation for the infrequent occurrence lies in the fact that surgical transection of the cervix is performed below the level of the internal os where Gärtner's duct rests are most frequently encountered.

#### CASE REPORT

The solitary specimen showing Gärtner's duct was from Mrs. B. S., aged 35 years (31,722), who was admitted with complaints of vaginal discharge and backache. A lacerated pelvic floor and cystoectocoele were encountered. The cervix was large, lacerated, and markedly eroded. Operation performed Jan. 23, 1937, consisted of amputation of cervix, anterior and posterior colpoplasty, and vaginal

Pelvic examination revealed a nulliparous introitus. The uterus was enlarged as outlined above and contained numerous fibroids. On Feb. 6, 1937, supra-cervical hysterectomy and bilateral salpingo-oophorectomy were performed. As the site of transection was close to the portio, a large segment of vaginal cervix and the entire supravaginal cervix was included. Gross and microscopic examination of the cervix revealed no special abnormalities. However, lying in the inner muscle fasciculi of the supravaginal cervix was a duct coursing parallel and close to the endocervix. It widened slightly in its descent. At its upper and lower portions, its lumen was irregular due to the formation of short papillas and the appearance of the irregular funnel-shaped incisurae. At either extremity lay collections of gland spaces, some of them encroaching upon the endocervix proper. The main duct presented a solitary layer of cuboidal cells. The cell membrane was not sharply defined. The cytoplasm was relatively scant and pale. The bulk of the cell body was filled by a round nucleus vesicular in character containing fine chromatin granules. The wide incisurae and gland spaces presented a similar lining epithelium. The glands presented a varied form. Some were round or oval, others showed papillary formation or were irregularly branched. Several contained deeply staining acidophilic secretion. The fine terminal glands which lay at some distance from the main duct were generally small in size but presented the characteristic epithelium. The stroma immediately subjacent to the main duct was comprised of cellular connective tissue but the terminal branches and glands were scattered in the fibromuscular layer.

#### ADENOMATOID HYPERPLASIA

Adenomatoid hyperplasia of Gärtner's duct glands has been infrequently recorded in the literature. In 1907, Robert Meyer, reporting detailed studies of normal Gärtner's duct rests in the human embryo, observed adenomatoid and papillary proliferation in the ampulla of the duct of a seven months' fetus. Rockstroh in 1935 reported two other cases of adenomatoid hyperplasia. In the first patient the lesion grossly consisted of small cysts occupying the cervix. Histologically the glands of varied size were lined by cuboidal cells. In the second case, a cervical polyp was removed and in addition biopsy of the cervix was performed. In the biopsy section, the proliferating glands of Gärtner's duct were accidentally found.

Two cases of adenomatous hyperplasia of Gärtner's duct rests have been noted in our laboratory studies.

The first, Mrs. A. N., aged 39 years (No. 24,044), was admitted to the Long Island College Hospital, Jan. 4, 1933, complaining of dysmenorrhea. Appendectomy was performed seventeen years ago without incident. A second laparotomy for supposed pelvic disorder was performed two years prior to admission. The menses which have always been regular, began at thirteen, recurred every twenty-eight days and lasted for two to three days. The patient had been married for fifteen years. The first pregnancy terminated in a spontaneous abortion at two months. The second pregnancy ten years ago was uneventful. The present illness began seven months ago and was described as pelvic pain starting with slight cramps the day prior to onset of flow, progressing in severity during the period, and persisting for four to five days after cessation of the menses. Vaginal examination revealed a parous introitus with good anterior and posterior walls.

The cervix was enlarged, firm and lacerated. The body of the uterus was slightly enlarged and contained several small fibromyomas which were irregularly distributed in the fundus. These were insensitive. The tubes and ovaries presented no apparent pathology. The posterior fornix contained two small nodules about  $1\frac{1}{2}$  cm. in diameter, which impinged upon the posterior wall of the cervix just above the cervicovaginal junction. They were sensitive and pressure upon

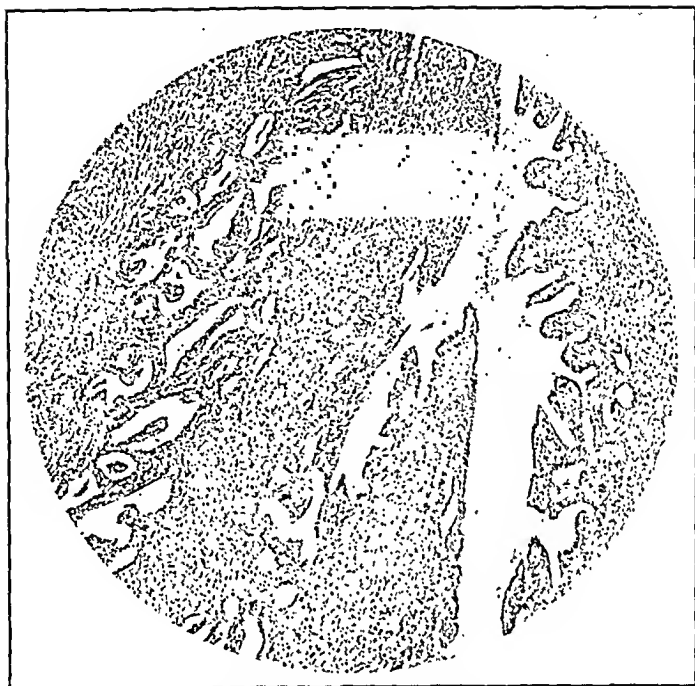


Fig. 2.— $\times 80$ . Gartner's duct, branches, and terminal glands are reproduced. Note the intraluminal papillae. The solitary layer of cuboidal cells is characteristic.

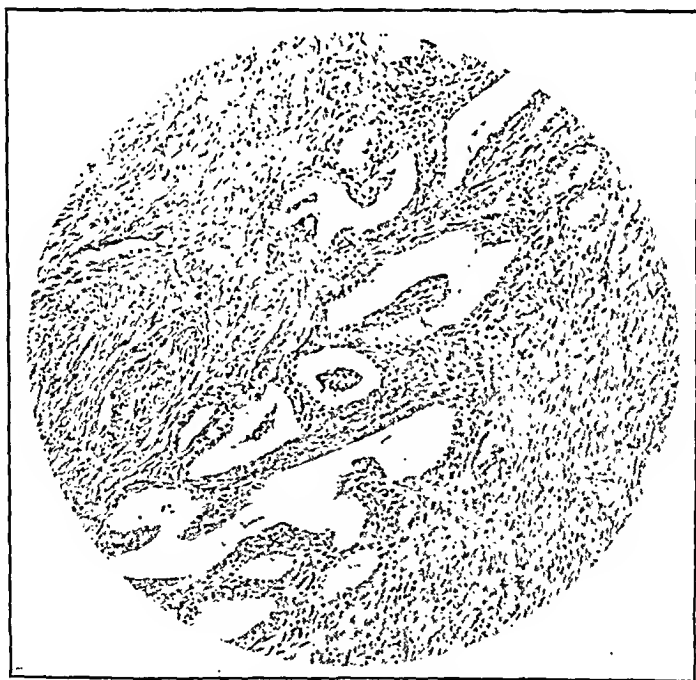


Fig. 3.— $\times 200$ . Glands of Gartner's duct origin. Round, oval, and papillary forms lie in the fibromuscular wall of the cervix. The lining cells are cuboidal or low columnar and contain faintly staining cytoplasm. The round pale nucleus almost fills the cell body.

in June, 1933. This was followed by amenorrhea and gradual involution of the cul-de-sac nodules, thus indicating their relation to pelvic endometriosis rather than to aberrant Gärtner's duct remnants in the supravaginal cervix. Adenomatoid hyperplasia of Gärtner's duct was only incidental. The large numbers of glands, their small size and deep-staining nuclei were all indicative of true proliferation of Gärtner's duct rests, rather than retention of incompletely involuted normal segments observed in the two previous cases.

The second case of hyperplasia was found in the cervical polyp of Mrs. L. F., aged 47 years (No. 33,815), who was admitted to the Long Island College Hospital, Feb. 13, 1937, complaining of vaginal bleeding. The previous history was uneventful. Menstruation began at fourteen, recurred regularly every twenty-eight days and continued for three to four days. The patient had been married for twenty years. There were seven pregnancies. Five terminated in normal

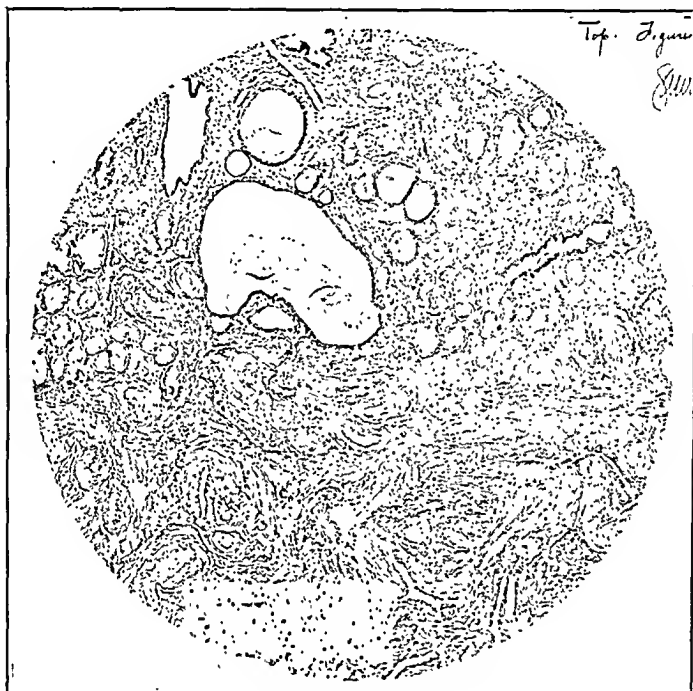


Fig. 5.— $\times 80$ . Adenomatoid hyperplasia of Gärtner's duct glands in a submucous fibroid. The fibromuscular matrix of the myoma is covered by a layer of endometrium. Lying between the muscle fibers and extending into the mucosa are large numbers of small, pale, round, or oval glands, frequently containing secretion. They present a solitary layer of cuboidal or low columnar cells with pale-staining cytoplasm and a small vesicular nucleus. Note the irregular endometrial glands with tall deeply staining nuclei.

full-term deliveries, two in spontaneous uncomplicated abortions. The present illness began one year prior to admission and consisted of prolongation of the menstrual flow associated with cramplike pain in the right lower abdomen. The physical findings were essentially negative. Pelvic examination, however, revealed a lacerated pelvic floor with moderate cystoecetocle. The cervix was irregularly lacerated, fixed in the vault and presented a polyp which was just visible in the dilated cervical canal. The uterus proper was small and posterior. The laboratory data were essentially negative. On Feb. 15, 1937, the polyp was removed. This was followed by curettage and insertion of radium. Upon pathologic examination, the curettings showed multiple endometrial polyps. The large polyp noted in the cervical canal measured 25 mm. in length, 14 mm. transversely at the tip and 4 mm. transversely at the site of transection. It was firm in consistency and upon cut section was gray white and fibrous. Microscopically,

them produced the subjective discomfort noted by the patient during menses. Operation on January 5 consisted of curettage and amputation of the cervix. The nodules in the cul-de-sac were not removed. Upon pathologic examination, the curettings showed classical changes of premenstrual endometrium. The amputated cervical cone measured 25 mm. in length, 35 mm. transversely at the portio, and 10 mm. transversely at the apex. The external os was lacerated. The squamous lining of the portio was normal. Just within the external os there were three small Nabothian cysts. The endocervix presented no other abnormalities. The muscle was fibrotic. Microscopically, the squamous lining of the portio presented hyper- and parakeratosis. The underlying connective tissue showed a slight exudate of lymphocytes and occasional plasma cells. The glands of the endocervix were hypertrophied and actively secreting. The stroma was edematous and also presented occasional lymphocytes and plasma cells. The fibromuscular wall showed advanced atrophy of the muscle fasciculi which were

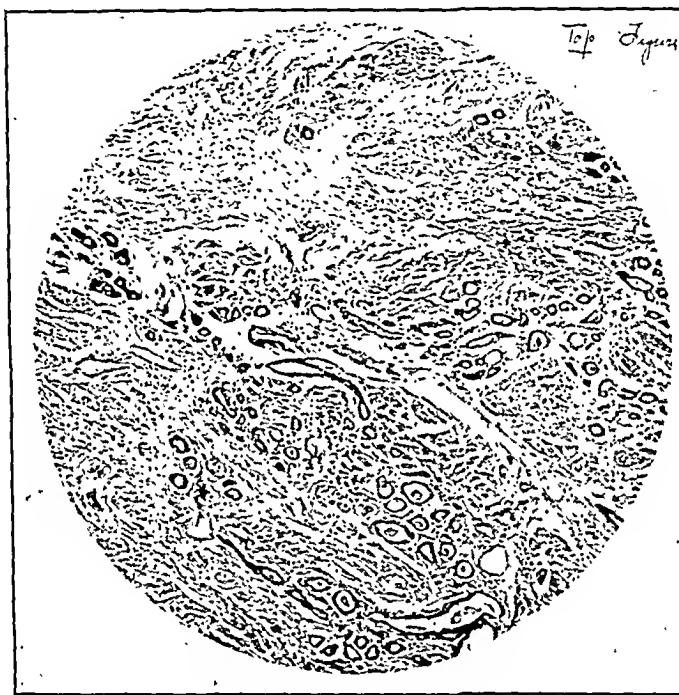


Fig. 4.— $\times 80$ . Adenomatoid hyperplasia of Gärtner's duct. The muscle layer of the cervix contains proliferating glands which are round, oval, or somewhat crescentic. Several contain secretion. The solitary layer of low columnar cells presents oval dark-staining nuclei. Flat and cuboidal cells, however, are encountered in some of the glands.

largely replaced by hyalinized connective tissue. At the apex of the cone about 2 to 3 mm. from the endocervix, the posterior lip contained collections of glands in its fibromuscular stratum. They were generally small, but some of moderate caliber were irregularly intermingled and suggested terminal branches of Gärtner's duct (Fig. 4). The glands were round, oval, or slightly elliptical in shape and presented a solitary layer of epithelial cells. These were generally low columnar but cuboidal, and flat endothelial forms were also present. The cell membrane was poorly defined, the cytoplasm scant and pale. The oval or elongated nucleus filled the cell body and though vesicular, stained intensely, showing a dense chromatin net work. Secretion was not uncommonly encountered. The gland collections, though somewhat radially grouped about the terminals, were separated by muscle and connective tissue fibers which were edematous. The postoperative course was uneventful. Relief from comenstrual pain, however, was not obtained and accordingly two x-ray treatments were administered



terminated in the birth of living twin girls. Examination six weeks post partum revealed a good pelvic floor and anterior wall. The cervix was slightly lacerated. The uterus in the second degree retroversion was fairly well involuted. A pessary for displacement was refused. On Sept. 6, 1933, the patient presented herself for examination, complaining of constant pain in the right lower quadrant and discharge. The vaginal mucosa was slightly injected. The uterus was in the first degree retroversion. The right ovary was palpable. A nodule the size of a hazelnut was noted along the course of the right uterosacral ligament and was fused with the posterior aspect of the supravaginal cervix. On Oct. 20, 1933, the discharge had cleared but pain persisted. Pelvic examination revealed a definite increase in the size of the nodule at the junction of the cervix and right uterosacral ligament. A second nodule was now also palpable to the left and slightly above the node previously noted. The patient was referred to the hospital with the diagnosis of "adenomyoma of the cul-de-sac and reetovaginal septum."



Fig. 6.—X80. True adenoma of Gärtner's duct. The tumor is comprised of a matrix of hyalinized connective tissue and involuntary muscle in which are embedded large gland spaces filled by numerous broad papillas.

Upon admission the above findings were confirmed. Proctoscopic examination showed a pale, glistening rectal mucosa. The blood vessels, however, were engorged. A diagnosis of "extrarectal neoplasm" was made. On Dec. 30, 1933 a barium enema showed no obstruction, dilatation or irregularity of the bowel. The laboratory data were negative. Operation was performed Jan. 2, 1934, under gas-oxygen anesthesia. A transverse incision was made through the vaginal mucosa at the junction of the cervix and posterior vaginal walls, exposing the subperitoneal areolar tissue. Three nodules were found in this zone. They lay in the muscle coat of the supravaginal cervix, but their external surfaces projected into the areolar tissues inferior to the cul-de-sac peritoneum. They varied from 1 to 2½ cm. in diameter and were firm, lobular, and fixed. Removal was difficult and required excision of a zone of contiguous cervical muscle. Five gold-screened radon seeds of 1 millieurie each were inserted into the bed of the nodules. The vaginal mucosa was approximated after a narrow iodoform gauze drain was left in situ for screening purposes.

it presented an endometrial lining which, however, was only focally encountered. At the tip it was replaced by infected granulation tissue. Where retained, the mucosa presented a lining layer of columnar epithelium, resting upon an underlying zone of edematous embryonal connective tissue. This supported occasional glands which occurred at irregular angles from the surface. They were of moderate size and generally round or oval in contour, but cystic, saccular, and irregularly branched forms, were also present. The lining cells of the glands were columnar and nonciliated. The cell membrane was poorly defined, the cell cytoplasm scant. The nucleus filling the cell body was oval or fusiform in shape and stained deeply. The bulk of the polyp, however, consisted of smooth muscle fibers concentrically arranged about large numbers of arterioles and venules. Sheaths of muscle and connective tissue cells also interdecussated at irregular angles. About the middle of the polyp but limited to only one of its surfaces, the muscle zone presented collections of proliferating glands which encroached upon the endometrial lining (Fig. 5). The individual glands though separated by muscle and connective tissue fibers were radially arranged about wider duct branches often filled with deeply staining secretion. These were lined by flat or low cuboidal epithelial cells. The gland spaces were small, round, oval, or slightly tortuous in form. The lumina were of varied dimensions and often contained acidophilic secretion. The lining cells varied from cuboidal to the low columnar type. The cell membrane could occasionally be identified. The cytoplasm was scant and stained faintly. The vesicular pale nucleus which was round or oval in form almost filled the entire cell body, but contrasted sharply with the deep-staining oval or fusiform nuclei of the endometrial glands. Histologically, therefore, the polyp was a small submucous fibroid clothed by endometrium. Gärtner's duct terminals and glands were found in the muscle zone and encroached upon the mucosa. Their relation to the submucous fibroid is difficult to estimate. Most likely pressure by proliferating tumor cells caused hyperplasia of Gärtner's duct rests, accidentally located in the zone of myomatous growth.

#### TUMORS OF GÄRTNER'S DUCT ORGAN

Benign tumors of this group are extremely rare. W. Rust records such a case accidentally encountered in a biopsy section from the cervix. About 0.5 cm. above the portio, the cervical muscle contained glands reminiscent of the sweat gland type. They varied from the size of a capillary lumen to cystic structures recognizable to the naked eye. Round, oval, papillary, and irregular saccular forms were present. These were lined by a solitary layer of epithelium of cuboidal form with translucent cytoplasm and a large nucleus which filled the cell body.

Malignant tumors of Gärtner's duct origin are recorded with slightly greater frequency. A case of cervical adenocarcinoma of this histogenesis was reported by Robert Meyer in 1907. G. A. Wagner also recorded a similar tumor in 1929. Rockstroh in 1935 also reported a malignant neoplasm of Gärtner's duct type. There was good response to radium.

No specimen of malignant Gärtner's duct tumor of the cervix was encountered in our laboratory. The clinical and pathologic characters of a benign papillary adenoma of Gärtner's duct origin is recorded in the case of Mrs. P. K., age 31 years (16,200), admitted to the Brooklyn Jewish Hospital, Dec. 28, 1933, complaining of pain in the right lower quadrant. The family and past personal history was essentially negative. Menstruation began at age of 15, recurred irregularly every six to eight weeks, and lasted for four to five days. The flow was associated with severe comenstrual pain which incapacitated the patient on the first day. There was little change in menstruation after her marriage in June, 1925. The first delivery in 1927 terminated in a stillbirth at term. The second confinement on June 23, 1930, was three and one-half weeks premature, and

spread of the lesion. The right posterior aspect of the portio and supravaginal cervix was shotty and nodular. Biopsy and further radiation were refused. Examination in April, 1939, showed further spread of the nodules which now involved the entire posterior aspect of the cervix. Additional treatment was refused.

#### SUMMARY

Gärtner's duct represents the persisting distal segment of the mesonephric or Wolffian duct. In the adult female it is rarely retained in toto. Segments are most frequently found in the supravaginal cervix. In specimens of cervix obtained by amputation, rests are uncommon. One instance was observed in 1,413 cases. The microscopic appearance is distinctive. Rests produce no symptoms or pathologic changes and are accidentally discovered. Adenomatoid hyperplasia may similarly be only a laboratory finding. Two cases are herein recorded. A case of papillary adenoma of Gärtner's duct origin has been observed. The symptoms, physical findings and pathologic features are noted. A five-year observation period reveals slow but progressive spread of the lesion.

My sincere thanks are herewith expressed to Drs. Alfred C. Beck, William A. Jewett, and Leo S. Schwartz for permission to include their cases.

1530 PRESIDENT STREET

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### MESONEPHROMA OF THE OVARY

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A SATISFACTORY classification of ovarian tumors has not yet been established, although much has been accomplished recently by correlating the clinical and pathologic features of these neoplasms. In reviewing over 350 true neoplasms of the ovary, a group of 6 has been separated on the basis of their pathologic characteristics. Schiller has recently described a similar group of cases and believes them to be derived from mesonephric tissue. It is the purpose of this paper to describe the clinical and pathologic characteristics of these tumors and to discuss their histogenesis.

#### CLINICAL CHARACTERISTICS

There are no symptoms which distinguish these tumors from other ovarian neoplasms. All 6 cases occurred after the age of 40. A mass in the abdomen or abdominal enlargement was a frequent complaint. Abdominal discomfort was sometimes noted.

Abnormal uterine bleeding, which is an important aid in classifying ovarian tumors, was usually absent in these cases. In one case there had been slight

The pathologic report of the excised nodules was as follows: "The specimen consists of three firm ovoid tissue masses varying from 1 to 2½ cm. in diameter. They are surrounded by loose areolar tissue. On section they are gray white, largely fibrous. Small areas present a granular appearance. Microscopically, all nodules are similar and present a matrix of connective tissue and occasional involuntary muscle fibers. The matrix supports bizarre proliferating glands (Fig. 6). The majority shows papillary configuration. The broad stromal core is lined by a solitary layer of low columnar or flattened epithelium (Fig. 7). The individual cell is small in size. The cytoplasm is scant. Cilia are lacking. The nucleus which is round or oval in form is small in size, vesicular, and contains fine chromatin granules. The nutrient capillaries are small. In other areas the matrix contains simple gland spaces lined by flattened epithelial cells as noted in the papillary zone. Secretory activity is lacking. Diagnosis: papillary adenoma of cervix, histogenesis uncertain." Since intestinal and uterine struc-



Fig. 7.—X120. True adenoma of Gärtner's duct. The finer structure of a papillary process is shown. The lining epithelium consists of a solitary layer of flattened or low cuboidal epithelium with a poorly defined membrane and scant pale cytoplasm. The nucleus is vesicular and almost fills the cell body. The stromal core is comprised of fibroblasts.

tures were not reproduced, a diagnosis of "Gärtner's duct adenoma" was made by exclusion. This opinion was confirmed by Dr. James Ewing who kindly reviewed the slides. The occurrence of the tumor nodules beneath the level of the cul-de-sac peritoneum and their intimate association with the cervix certainly supported this viewpoint.

The postoperative course was uneventful, but examination upon discharge showed induration in the posterior and right lateral walls of the cervix. The vaginal wound was healed except for granulation tissue at the site of the drain. When seen Feb. 7, 1934, the patient was free from subjective complaints. Recto-vaginal examination showed a persistent but slight induration on the posterior and right lateral walls of the cervix. The uterus retained its retroverted position. The adnexa were negative. On March 13, 1935, the patient was symptom free, but the nodules were evidently recurring on the right posterior lateral aspect of the supravaginal cervix. In November, 1937, examination showed progressive

4. These tumors may also occur at the site normally occupied by the mesonephric remains; namely, the broad ligament. One example of this site of origin is included in Schiller's paper.

The Cohnheim theory concerning the role of embryonic "cell rest" tumor development has been greatly narrowed in its application in recent years. However, there is a striking resemblance between the cells of the ovarian tumors



Fig. 1.—Case 1. A low power view of a solid mesonephroma, showing the characteristic small cysts and tubules lined by an endotheliallike cell with projecting nuclei.

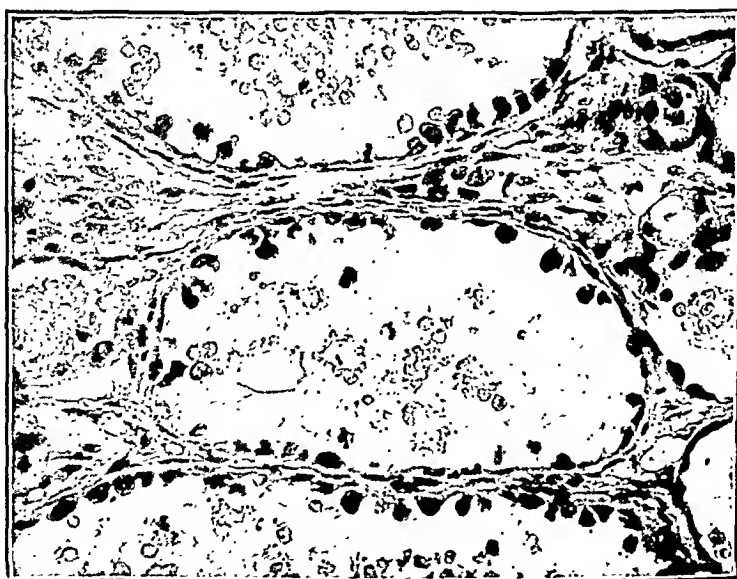


Fig. 2.—Case 2. This is a solid mesonephroma, showing the characteristic flat-lining cell with projecting nucleus.

irregularity in the periods for about one year, but in this case there were myomas. In an additional case there was uterine bleeding for one week in a patient several years past the menopause, but here the tumor was highly malignant with extensive pelvic involvement and extension into the uterine cavity probably occurred. The absence of abnormal uterine bleeding is in keeping with Schiller's findings.

### PATHOLOGY

The tumor may be practically solid, with numerous irregular fluid-filled spaces or may be cystic with papillary projections. Grossly, the latter form is indistinguishable from the common Müllerian papillary cystadenoma. In the present series, 4 are of the solid and 2 of the cystic variety. The largest tumor in the group measured 25 cm. in diameter and the smallest 12 cm. in its greatest diameter. In 4 of the tumors the external surface was smooth, but in 2 the capsule was penetrated by growth. The solid tumors can readily be distinguished from the cystic, but the microscopic similarity of the cells suggests a similar origin.

The solid tumors are composed of microscopic cysts or tubules lined by an endothelial-like cell (Fig. 1). These cells are characterized by sparse cytoplasm and projecting nuclei (Fig. 2), and closely resemble those of the mesonephric glomerulus (Fig. 3). In some areas flattening may be carried to an extreme degree, so that the cells bear a striking resemblance to the endothelial cells of the blood vascular system (Fig. 4). There is a tendency for the tubular spaces to be bridged or filled by a growth of lining cells (Fig. 5). Schiller has commented on this as an attempt at glomerular formation, thus supporting the theory of nephritic origin. It is true that the tiny projections may contain capillary loops, but the resemblance to glomeruli is certainly not striking. In still other areas, the tubular characteristics may be lost, and the tumor cells spread out in an irregular manner through the connective tissue framework (Fig. 6).

The connective tissue may be abundant and is characterized by collagenous fibers with relatively few spindle-shaped cells. In other areas the connective tissue may be very sparse, so that the basement membranes of adjoining tubules are in apposition. Hyalinization is a striking characteristic, giving some areas an almost cartilaginous appearance (Fig. 4).

The cystic tumors reflect their papillary tendency in the microscopic architecture. There may be multiple, branching, connective tissue stalks lined by the characteristic endothelial-like cells with bulging nuclei (Fig. 7). The projecting nucleus and the relatively sparse cytoplasm are distinguishing characteristics of the tumor cell.

### MALIGNANCY

Of the 6 patients, 2 died of recurrence in about six months. Both of these were of the solid variety. Each of the remaining patients is well at 2, 9, 9, and 14 years following operation. In the 2 fatal cases, the gross appearance of the tumor strongly suggested malignancy, for in each instance the capsule was penetrated by tumor cells. The tumors in the remaining cases were well encapsulated.

### HISTOGENESIS

For purposes of classification, the histogenesis of these tumors is of interest. For the following reasons, Schiller believes them to be derived from mesonephric rests which have become included in the ovary.

1. The tumor cells resemble the endothelial cells of glomeruli (Fig. 3).
2. The tumors contain isolated structural units which resemble glomeruli. These mesonephric glomerularlike structures are thought to be mesonephric because they contain only a few capillary loops. The mesonephric glomerulus contains but a few loops and is embryologically more closely related to the ovary than either the pronephros or the metanephros (Fig. 8).
3. Tubules are found in the tumors. These might correspond to the tubules of the mesonephros.

tubular structures which might represent mesonephric tubules. On the other hand, there is nothing about these tubules to indicate a mesonephric origin. In the present series, all tumors have apparently arisen in the ovarian tissue, so that we have not had the opportunity to study a case which has arisen in the broad ligament.

There is one other point which might indicate the embryonic, but not necessarily the mesonephric origin for these tumors. According to Popoff, at certain embryologic periods, the right ovary is found to be less differentiated than the

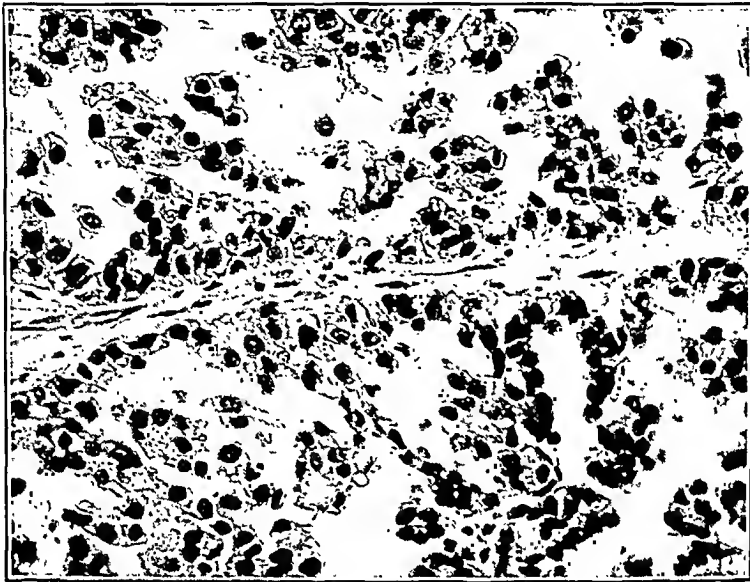


Fig. 5.—Case 4. A high power view of a solid mesonephroma showing the tendency of the cells to bridge the tubular space. In other areas the tubules were completely filled with tumor cells. This patient is well, but only two years have elapsed since operation.

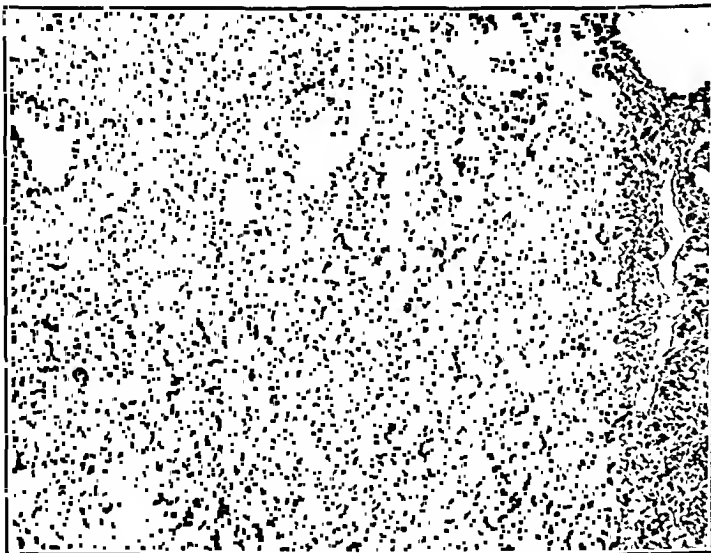


Fig. 6.—Case 3. A low power view of a solid mesonephroma, showing the tumor cells scattered irregularly through the supporting stroma. In the upper portion of this section may be seen the characteristic cystic structure with flat cells and projecting nuclei.

under discussion and the cells of the mesonephric glomerulus (Fig. 3). On the other hand, it has been most difficult to identify structural units in the tumor tissue which might be taken for distorted glomeruli. As mentioned above, the tumor cells show a tendency to grow into the lumina of the tubules or cysts, but, in our opinion, there is no true resemblance to glomeruli. It is true that the papillary projections of the tumors contain capillaries, but one would expect to find this in any papillary neoplastic growth. However, there are numerous

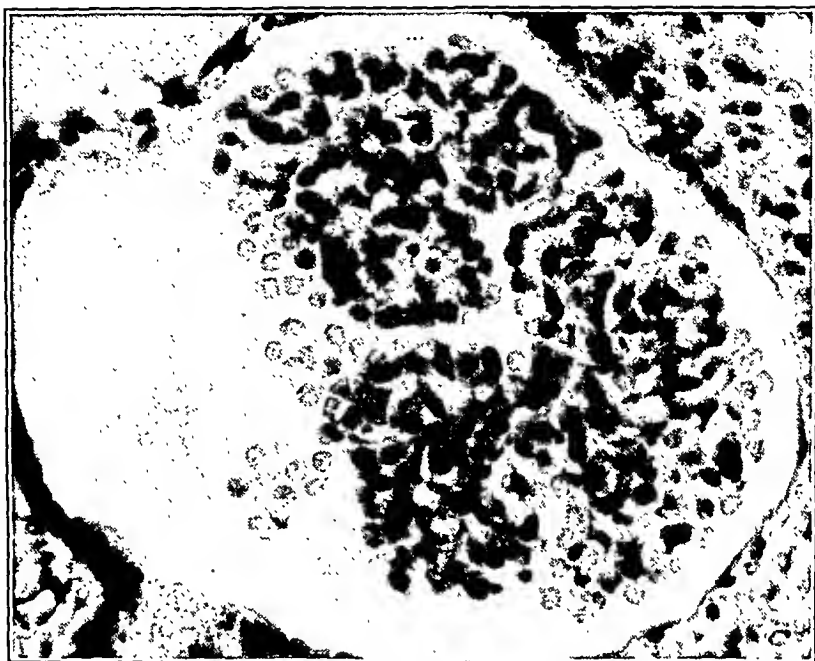


Fig. 3.—A mesonephric glomerulus. A coronal section through a 14.5 mm. human embryo. These cells are considered by Schiller to be the cells of origin for the tumors under discussion. He has therefore called them mesonephroma.  $\times 600$ .

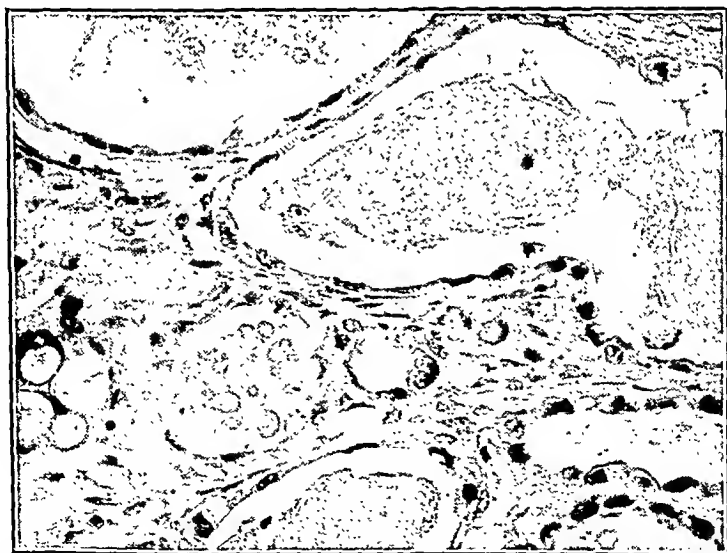


Fig. 4.—Case 2. A high power view of a solid mesonephroma, showing the flattening of the tumor cells that may sometimes occur. These resemble the endothelial cells of the lymph or blood vascular system.



Microscopically, this tumor was composed of small tubules, and in the illustration the cells show a tendency to overgrowth (Fig. 1).

Patient died of recurrence within six months.

CASE 2.—(C. H. I. Path. 10676.) A 41-year-old woman had noticed a mass in the lower abdomen for about two months. For the past year there had been slight irregularity of the menstrual periods. Seven years previously she had had a bilateral salpingectomy. On March 6, 1930, a supravaginal hysterectomy and right oophorectomy were performed. The left ovary appeared normal and was not removed.

The uterus measured 6 by 5 by 4 cm. There were intramural myomas measuring up to 3 cm. in diameter. The right ovarian mass measured 15 by 12 by 8 cm. Section through the mass showed the entire tumor filled with a soft edematous very cellular tissue of yellowish color. The microscopic appearance is seen in Figs. 2 and 4.

Patient is living and well nine years after operation.

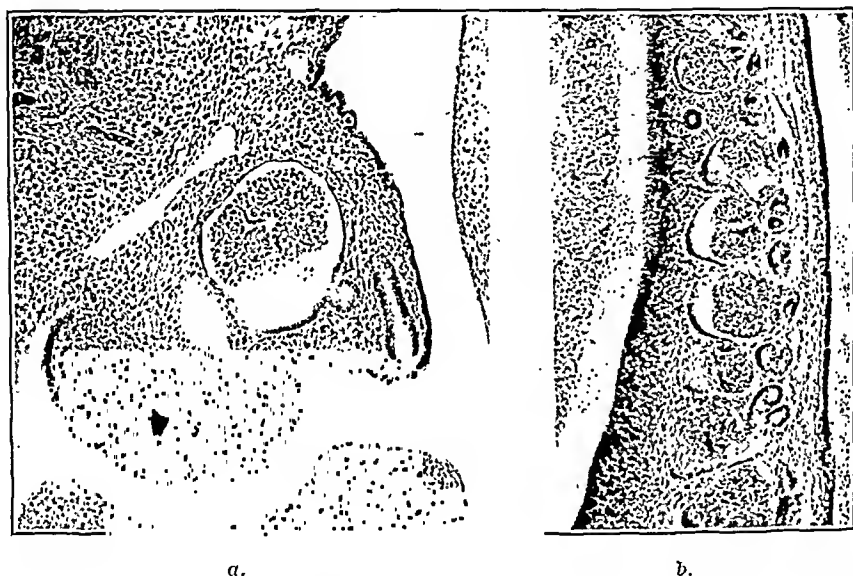


Fig. 8.—(a) This is a coronal section through a 14.6 mm. human embryo. This shows the proximity of the mesonephros to the genital ridge and indicates the possibility for mesonephric cells to become mingled with the cells of the developing gonad.  $\times 150$ . (b) A sagittal section through a 12.0 mm. human embryo again illustrating the proximity of the mesonephros to the genital ridge.

CASE 3.—(C. H. I. Path. 19787.) A 58-year-old woman complained of diarrhea of two months' duration. Two months ago she had slight vaginal bleeding for one week. There had been no recurrence of this. For the past month she had had some lower abdominal pain. There was a hard mass in the lower abdomen extending to the umbilicus. On May 2, 1938, the left tube and ovary and the right ovary were removed. There was extensive pelvic involvement and nodules were felt in the liver. A small nodule was removed from the peritoneum.

The right ovarian specimen measured 12 by 10 by 8 cm. The surface was smooth. The attached tube appeared normal. The mass was soft and edematous and on section showed irregular cystic spaces containing clear uncoagulated fluid. The left ovary measured 4 by 2 by  $1\frac{1}{2}$  cm. It has a cellular appearance and showed some papillary nodules with a structure similar to that seen in the large mass from the opposite side. The microscopic appearance is shown in Fig. 6.

Patient died within six months of recurrence.

CASE 4.—(C. H. I. Path. 19112.) A 72-year-old woman entered the hospital complaining of a mass in the lower abdomen. She had noticed this for about four months. Normal menopause twenty-two years before. There had been no bleeding

left, and in birds the right ovary is present only in a rudimentary form. Therefore, one might expect the right ovary to contain more embryonic remnants. If this were so, there should be more tumors arising from the right than from the left side. Such is the case. In the 6 cases herein reported only 1 was present solely in the left ovary, and in Schiller's series there was but 1 out of 10 cases similarly located. Seegar has also found that other tumors thought to arise from embryonic rests, for example dysgerminoma, are much more commonly found in the right ovary. However, this evidence is no more than suggestive.

The theory of the mesonephric origin of these tumors while plausible is not yet proved.

#### SUMMARY

From a series of 350 ovarian neoplasms, 6 cases have been described with distinguishing pathologic features. The tumors occurred after the age of 40 and presented no characteristic clinical features. Two were found to be malignant and 4 were benign. The mesonephric origin of these tumors has been discussed.



Fig. 7.—Case 5. A low power view of a cystic mesonephroma. Grossly this tumor could not be distinguished from a common ovarian papillary cystadenoma. However, its lining cells indicate that it should be classified as a mesonephroma. This patient is well fourteen years after operation.

#### CASE HISTORIES

CASE 1.—(C. H. I. Path. 8710.) A 63-year-old woman was admitted to the hospital for the removal of a mature cataract. During the routine examination a mass was felt in the lower abdomen and operation was advised. Menopause was several years previously and there had been no bleeding since. At operation March 19, 1928, a mass extending almost to the umbilicus was freed from the bowel. A right salpingo-oophorectomy was performed.

The specimen measured 13 by 10 by 7 cm. and retained the shape of the ovary. The fimbriated end of the attached tube was closed, but otherwise appeared normal. The surface of the ovary showed a nodular appearance with variegated colors of red and yellow. In several places the capsule had been penetrated and a squatty cauliflower growth protruded. The cut surface of the tumor showed a yellow partially necrotic center with islands of opaque gray and small patches of hemorrhage.

cervix, fornices, and external os.<sup>1, 2, 3</sup> Most of the preparations used heretofore for this purpose were not very effective in their action. Since the action of these substances was so effective as a cleanser, and therefore, as an aid to diagnosis, the following study was undertaken to investigate their action and effectiveness when used as a cleanser in the form of a vaginal douche.

When applied to the vaginal walls, cervix, fornices and external os, aluminum hydroxide gel and colloidal kaolin immediately coagulate any mucus or debris with which they come in contact, and this coagulated mass is readily removed by rinsing with water. Complete removal of this masking mucus was found to facilitate diagnosis by increasing visibility of underlying tissue to a degree we have not observed previously with other cleansing agents.

Aluminum hydroxide and colloidal kaolin were compared with other substances which have been used to remove vaginal and cervical debris and mucus. These substances are water, normal saline, hypertonic saline, sodium bicarbonate, tincture of green soap, proteolytic enzymes, silver nitrate, various mercurial antiseptics, 5 per cent solution lysol, and gentian violet. The first four substances have only such mucus removing properties as can be attributed to the mechanical action of flushing and so remove mechanically some of the debris present in the vaginal cavity without acting on the mucus which adheres to the tissues. Tincture of green soap also removes some of the vaginal debris but does not dislodge the mucus on the tissues. It slides over this mucus without affecting it in any way except by the mechanical scrubbing employed in its use. Furthermore, tincture of green soap is quite irritating to tender and eroded vaginal tissue; this irritating action is increased when the vaginal tissues are scrubbed with this substance. The proteolytic enzyme preparations have some action in digesting mucus but their use is rather cumbersome, requires considerable time, and the method of application is such that all portions of the vaginal tract cannot be reached effectively. Silver nitrate, because of its corrosive nature, is not to be recommended in cleansing the vaginal tract. The other antiseptics used vary little from the action of water. The use of an antiseptic on mucous coated vaginal tissue may be ineffective because the antiseptic must first penetrate the mucus in order to reach the tissues. If the antiseptic used does penetrate this mucus, its action may be so changed as to have very little or no effect upon the tissues. Aluminum hydroxide has none of the objectional qualities of the above mentioned substances, and to date has been used satisfactorily in over four hundred patients, as an aid to diagnosis by removal of vaginal and cervical mucus and debris, and in 120 cases as a simple cleansing vaginal douche.

TABLE I

CONDITION	NO. OF CASES	TIMES PER WEEK	NO. OF WEEKS	RINSING
Nonspecific leucorrhea	21	4	3	Morning
Leucorrhea due to mild cervicitis	14	7	4	Morning
Leucorrhea due to moderate or marked exocervicitis	8	7	4	Morning
or endocervicitis	11	7	4	Morning
Pretherapeutically in trichomonas vaginitis	12	4	1	Morning
Pretherapeutically in moniliasis	5	4	1	Morning
Salpingitis (with hot water), 2 oz. to 2 qt.	6	3	Indefinitely	Morning
Chiefly as a measure in vaginal cleanliness	43	3	Indefinitely	Morning or immediately

This mucus-coagulating effect of aluminum hydroxide and colloidal kaolin may be strikingly demonstrated in vitro by adding it to a 5 per cent solution of gastric mucin or to mucus removed from the body.

The above described action also takes place when the preparation is used as a vaginal douche. The patient is instructed to use one-half ounce of the aluminum

since. At operation on Oct. 14, 1937, large bilateral masses were shelled from the pelvis. The uterus was grossly normal and was not removed.

The left ovarian mass measured 16 by 14 by 10 cm. The capsule was well preserved. A normal appearing tube was thinned out over the surface. Section through the mass showed it to be solid cellular tissue with numerous cysts. The cysts were filled with a cloudy fluid. The right ovarian mass measured 11 by 7 by 5 cm. Its appearance was similar to that of the opposite side (Fig. 5).

Patient living and well two years after operation.

CASE 5.—(C. H. I. Path. 5748.) A 54-year-old woman entered the hospital complaining of lower abdominal discomfort and enlarging abdomen of three months' duration. She had a normal menopause eight years before. There had been no bleeding since. At operation April 9, 1925, a large cyst arising from the right ovary was found to fill practically the entire abdomen. This was tapped and removed by clamping the pedicle. The uterus contained a small myoma and was removed.

The excised cyst measured 25 cm. in the collapsed state. It was unilocular and the inner wall was studied with a cauliflower growth. The growth did not extend through the wall at any point. The microscopic picture was typical of the cystic form of mesonephroma (Fig. 7).

Patient is living and well fourteen years after operation.

CASE 6.—(C. H. I. Path. 11391.) A 45-year-old woman was admitted to the hospital because of a mass in the lower abdomen. She had lost 30 pounds in weight during the past six months. A normal menopause occurred 3 years ago. There had been no postmenopausal bleeding. At operation on Nov. 17, 1930, a large cyst of the right ovary was ruptured in delivery. A panhysterectomy and bilateral salpingo-oophorectomy were performed.

The ovarian cyst was thin walled and the inner lining was covered with numerous small papillary projections. There was one solid central portion. The uterus and other tube and ovary were normal.

The patient is living and well nine years after operation.

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## VAGINAL USE OF ALUMINUM HYDROXIDE AND COLLOIDAL KAOLIN

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THE need for a nontoxic, nonirritating vaginal cleanser has long been recognized. The preparations which are employed for this purpose are in most instances objectionable either because of corrosive nature, toxicity, irritating properties or general ineffectiveness. A suitable substance for this use should have none of the above properties and yet have the ability to remove the cervical and vaginal debris present in the vaginal tract. Aluminum hydroxide and colloidal kaolin\* have been used previously, as an application on cotton sponges, for the purpose of removing from the vaginal tract mucus which tended to obscure lesions present in the

\*Aluminum hydroxide gel 80.0 per cent, kaolin 19.0 per cent, sodium benzoate 0.5 per cent, mixed phenols 0.5 per cent (consisting of eucalyptol 1 part, menthol 1½ parts, and thymol 4 parts). Supplied through the courtesy of John Wyeth & Brother, Inc., Philadelphia, Pa.

# THE USE OF TESTOSTERONE PROPIONATE IN THE TREATMENT OF THE MENOPAUSAL PATIENT

## WITH A PRELIMINARY REPORT ON THE USE OF PELLETS OF CRYSTALLINE TESTOSTERONE PROPIONATE

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THIS report presents our experiences with the use of the so-called "male" sex hormone, testosterone propionate, in the treatment of the menopausal patient. The menopausal syndrome may occur during or after the transition period, at which reproductive function ceases. This phenomenon is a normal physiologic one, characteristic of the process of aging. The precipitating factor appears to be the withdrawal of estrogens, resulting from ovarian failure to respond to the pituitary gonadotropic hormone. Therefore, estrogenic substances have been administered for the relief of this syndrome. Estrogens, however, are not specific in this respect as other hormones, including progesterone (1), testosterone (2) and desoxycorticosterone (3) may act similarly.

The therapeutic rationale for the use of testosterone propionate has been fully reviewed elsewhere.<sup>4</sup> Suffice to say, testosterone is not only a powerful androgen but also a very potent gynecogen.

### MATERIAL AND METHODS

In the past year, fifteen menopausal patients, including two surgical castrates, have been treated with testosterone propionate. Their ages varied from 39 to 50 years. Because the degree of severity of symptoms depends a great deal upon the constitutional status of the patient, as well as upon environmental factors and intercurrent diseases, each case was carefully studied and only those diagnosed as having severe menopausal symptoms were accepted for treatment. Social service workers were called in when necessary to complete evaluation of the case. Appropriate sedation and whatever other medication was deemed necessary were prescribed, where needed.

### DOSAGE

The individual dosage used consisted of 5 mg. of testosterone propionate per cubic centimeter of sesame oil. Injections were given subcutaneously, usually in the deltoid region, sufficiently deep to cause no swelling in the overlying skin. At first, the hormone was given two to three times a week. With clinical improvement the injections were repeated at weekly, and then bi-weekly intervals. Therapy was maintained for four to six weeks after symptoms had disappeared.

Two additional methods of administration have been utilized. When the patient's symptoms were well controlled by subcutaneous injections of the hormone, tablets containing 5 or 10 mg. of testosterone propionate, combined with an enteric coated bile salt preparation, were prescribed for oral use. The other method consisted of the subcutaneous implantation of pellets of crystalline testosterone propionate; three to four pellets, weighing 6 to 9 mg. each, were embedded under the

hydroxide-colloidal kaolin mixture together with eight ounces of water in a hydrostatic bag. After cleansing with this mixture, the patient may rinse immediately with several quarts of warm water. If continued action is desired, the patient should not rinse for several hours after applying the mixture. This douche may be repeated as often as is desired without any harmful effect. The pH of the mixture is about 7.0 and supplies neither acid nor alkali to the vaginal tract. It is a neutral, mucus-coagulating, nontoxic, nonirritating substance. If acidity is desired therapeutically, it may be supplied by agents specifically for this purpose.

### RESULTS

Table I shows the types of condition in which this douche has been used. In this study there have been 43 patients who were given the douche chiefly as a measure in vaginal cleanliness, 21 patients in whom the leucorrhea present was due to a nonspecific infection (by nonspecific infection is meant infection due to organisms other than *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, and *Monilia albicans*), 14 cases of leucorrhea due to mild cervicitis, 12 cases of leucorrhea due to *Trichomonas vaginalis*, 11 cases of leucorrhea due either to moderate or marked endocervicitis, 8 cases of leucorrhea due to either moderate or marked exocervicitis, 6 salpingitis cases, and in 5 cases of leucorrhea due to *Monilia albicans*.

This table also gives the details of its use in the various conditions. In the trichomonas and monilia cases, where there is a marked tenderness present, due to either of these infections, and treatment cannot be started immediately, the use of the douche eases the irritation, so that the proper therapeutic measures can be taken. In the salpingitis cases the patient uses two ounces of the mixture to two quarts of hot water every other day for as long as is desired. All of the cases responded to this form of cleansing and showed improvement after its use. In none of the patients in whom the aluminum hydroxide-colloidal kaolin mixture has been used has there been any toxic or untoward reaction.

### SUMMARY AND CONCLUSIONS

1. The aluminum hydroxide-colloidal kaolin mixture has proved to be a valuable aid in establishing diagnosis of vaginal pathology and is an effective vaginal cleanser in the form of a douche.

2. It has been used successfully as a general vaginal cleanser, in cases of leucorrhea due to nonspecific infection, mild cervicitis, moderate and marked exocervicitis and endocervicitis, in cases of trichomonas vaginitis and monilia vaginitis as a pretherapeutic measure, and in cases of salpingitis.

3. The aluminum hydroxide-colloidal kaolin mixture may be used as often and as long as desired without any harmful effects.

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Knoll, W.: Do Athletes Have Difficult Labors? Med. Klin. 35: 845, 1939.

From a study of 73 married female athletes, the author concludes that individuals who participate in athletics do not have more difficult labors than women not interested in sports. A large proportion of the athletes who had children, took up their sport activities again soon after each labor. Likewise the author denies that women athletes are more often sterile than other women. Hence, young girls may safely indulge in all forms of athletic activities.

omitted. The 5 mg. tablets orally, without the bile salts, proved ineffectual and were discontinued. With the return of symptoms three pellets of crystalline testosterone propionate, totaling 22.2 mg., were implanted subcutaneously. Fifteen days later she experienced a scanty flow of uterine bleeding. She has now remained practically symptom free for two and one-half months, and the pellets are still palpable under the skin of her thigh.

CASE 3.—A forty-year-old, white housewife came to the dispensary complaining of increasingly severe hot flushes, insomnia, formication, poor appetite, and marked nervousness. She had undergone a panhysterectomy two months before. Physical examination, except for a moderate degree of deafness, otosclerotic in origin, was essentially normal. Pelvic examination revealed the absence of the uterus and adnexa.

Therapy consisted of 5 mg. of testosterone propionate twice a week subcutaneously. Relief became apparent in ten days. In three weeks, her flushes were considerably milder and her appetite had greatly improved. In a month, she was able to do her housework without tiring easily. Injections were now given once a week for six more weeks. Her flushes at this time occurred at intervals of two to three days and were very mild in character. She failed to return until one month after her last injection when she complained that her flushes were returning more frequently and with increasing severity. She was given testosterone propionate orally, combined with bile salts, 5 mg. daily for two weeks, then three times a week for three more weeks. Her symptoms were completely relieved and she has since remained practically symptom free (two months).

### RESULTS

The vasomotor phenomena, hot flushes, cold sweats, acroparesthesias, etc., were practically completely relieved in every case. The elapsed time before a satisfactory response was obvious, varied from ten days to three weeks. Remarkable, indeed, was the very early disappearance of lassitude, tiredness, easy fatigability and the rapid return to normal physical vigor. Concomitantly, the appetite improved as well as the general sense of well being.

Two patients with genitourinary complaints of urgency, urinary frequency, mild burning and nocturia, for which no pathologic basis could be ascertained, became practically asymptomatic during the treatment.

Three patients became tanned over the exposed areas of their body during the winter months.

Two cases with menopausal arthralgia received relief from their vasomotor phenomena but showed no improvement of joint symptoms until estradiol dipropionate was used alternately with the testosterone propionate.

The uterine bleeding that was apparently provoked in the second case, and which has been noted in two other cases in which pellets were implanted, remains inexplicable in the light of our present knowledge.

Although carefully watched for, no signs of masculinization of any sort whatsoever were noted. No effects upon libido were observed.

### DISCUSSION

The therapeutic value of testosterone propionate in the relief of the vasomotor phenomena associated with the menopause seems clearly established from both the results obtained in this series and those reported by others.<sup>2,6</sup> The *modus operandi* by which these symptoms are ameliorated is as yet obscure.

The route and method of administration play an important role in determining the total dosage necessary to secure clinical relief. When the hormone is given by injection, the subcutaneous route is preferable to the intramuscular one, as the subcutaneous route provides for a longer duration of action and thus is more effective per given dose.<sup>7</sup> When testosterone propionate is given orally, the effectiveness is so

skin through a No. 12 needle. The average total weight of the pellets per patient was approximately 25 mg. Although this method of administration was at first used in only those patients who had a recurrence of symptoms after cessation of therapy, it has now become the method of choice in all severe cases since it has yielded the best and most consistent results. Further studies, with the use of pellets only, will be reported in a later communication.

Where arthralgia was also present, estradiol dipropionate was alternated with the testosterone propionate until the joint symptoms disappeared.

The following case histories illustrate the method of approach used in the treatment of our menopausal patients.

CASE 1.—A white, married housewife, aged 48 years, whose menopausal symptoms began in the summer of 1937, appeared at the clinic complaining of severe flushes, followed by cold sweats, both day and night, headaches, blurring of vision and poor appetite. She had previously been treated with estrogenic substances with indifferent success. Physical examination revealed poor condition of her teeth; otherwise she was essentially negative. Pelvic examination was negative.

She was given 5 mg. of testosterone propionate subcutaneously twice a week for three weeks with such marked improvement that the interval between injections was increased to one week. Dental consultation was secured, she was given vitamin-B complex (brewer's yeast) to stimulate her appetite, and barbiturates for sedation. She became symptom free after six weeks and did not return until five weeks later, when she developed a severe upper respiratory infection accompanied by a return of her flushes. Therapy was repeated with the same success. A few weeks later when well regulated with 5 mg. of testosterone propionate once a week subcutaneously her flushes suddenly increased in frequency and severity. Inquiry revealed that many domestic difficulties had arisen at home. With the aid of the social service worker, the situation was adjusted, and her response to therapy once again became gratifying.

Whenever therapy was withdrawn for periods of three to four weeks, her symptoms rapidly reappeared. After one month without therapy, four pellets of crystalline testosterone propionate, totaling 26.1 mg., were implanted subcutaneously. In two weeks her flushes had entirely disappeared and since then (ten weeks) she has remained symptom free. With this form of therapy, she has felt much better than she had with the injections. It is interesting to note that she became tanned over the exposed portions of her skin, an observation previously reported in the male.<sup>5</sup> This phenomenon was observed in two other cases.

CASE 2.—A white, married housewife, aged 46 years, was referred to the gynecologic dispensary because of severe and frequent hot flushes, sweats, poor appetite, insomnia, urgency and frequency of urination. The past history revealed a story suggestive of gall bladder disease but was otherwise negative. Physical examination, except for moderate obesity, was within normal limits. Pelvic examination was negative. Suction biopsy revealed a slight proliferation of the endometrium. Blood and urine examinations were negative.

She was given 5 mg. of testosterone propionate subcutaneously twice a week. At the same time, a reducing diet was prescribed and barbiturates were given for sedation. With clinical improvement injections were reduced to one a week. Her urinary symptoms rapidly cleared with no special medication. She apparently had a normal menstrual period five weeks after therapy with the hormone had been instituted. (Her last menstrual period had occurred eight months before.) Suction biopsy at this time revealed a hypoplastic endometrium. Injections were continued; flushes, now occurring two to four times a day, were very mild. She developed la grippe four weeks later with a marked aggravation of her symptoms. Dosage had to be increased to 15 mg. ( $3 \times 5$ ) per week for two weeks in order to control her flushes. After another month, when well regulated, she was given daily oral doses of testosterone propionate, 5 mg., combined with bile salts. She was maintained thus for a week but at this time, proving sensitive to the bile salts, the latter were



# INTERNAL ENDOMETRIOSIS (ADENOMYOSIS) OF THE URINARY BLADDER

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**S**TARR JUDD, in 1921, described the first case of endometriosis of the bladder. Ottow, in 1927, succeeded in making the first correct preoperative diagnosis by cystoscopy. In the same year, Plaut made the diagnosis in the operating room and confirmed it by rapid frozen section. Since that time, the number of cases reported has increased slowly but steadily. After v. Mikulicz' survey in 1936, further cases have been described by Perlmann (1934), Weijtlandt (1934), Erle (1935), Chauvin (1936), Mark (1937), Adams, Stoeckel, Homma (1938), and Reynolds (1939).

The clinical picture of endometriosis of the bladder is well defined today. The same cannot be said for its histogenesis and pathogenesis. The case which I am reporting offers, in my opinion, several interesting features which may help to clarify some mooted points, particularly concerning histogenesis.

**CASE.**†—C. B., a 26-year-old female, was admitted to Beth Israel Hospital with a diagnosis of acute cystitis on Oct. 26, 1938. (Admission No. 106153.) Her chief complaint was suprapubic pain on urination.

**Menstrual history:**  $14 \times 3.7 \times 23$ . The patient had considerable dysmenorrhea, two days before and on the first day of menstruation. She had never missed a period. The flow was moderate. The patient was unmarried and had never been pregnant.

One and one-half years ago the patient was operated upon at another hospital. At that time a simple ovarian cyst was removed together with one tube and the vermiform appendix. There were no unusual findings.

Three days before admission, simultaneously with the onset of her menses, the patient noticed a sharp suprapubic pain and burning on urination. There was also an increase in frequency. No pain in back, no fever, no gross hematuria were noticed. These symptoms had been occurring off and on for the past year, their onset coinciding with that of the menses although they often lasted longer than the menstrual period.

Vaginally, a firm tumor on the right side of the uterus was felt anteriorly. Otherwise the clinical examination was negative.

**Urine.**—(Catheter specimen.) Specific gravity 1024, acid, bloody, albumin 1-plus, white blood count 8-10 per high power field, a few squamous epithelial cells. **Blood Count.**—3.89 million red blood cells, 8,000 white blood cells. Slight anisocytosis.

**Intravenous Urography.**—There was a large filling defect in the basal portion of the right side of the bladder. The filling defect was also seen in the cystogram.

**Cystoscopy.**—There was a bulging tumor on the right side extending from the sphincter margin backward to the posterior wall. The mucosa was not ulcerated. The tumor was the size of a quarter coin.

**Biopsy.**—Inflamed bladder mucosa with large epithelial nests of Brunn.

**Preoperative Diagnosis.**—Neoplasm. The pathologist (Dr. A. Plaut) on the basis of the history and cystoscopic findings, mentioned the possibility of an endometriosis of the bladder.

**Operation.**—(Dr. S. Wilhelm.) The peritoneum was opened, no implants were found. The bladder was opened and the tumor excised. It was round, elastic and situated in the right lateral wall, extending from the sphincter margin backwards

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†Thanks are due Dr. E. A. Horowitz for permission to use the clinical data.

enhanced by the simultaneous administration of bile salts,<sup>8</sup> that this method of therapy is discontinued if the bile salts are not well tolerated by the patient.

From our preliminary studies with the subcutaneous implantation of pellets of crystalline testosterone propionate, it is felt that this procedure will eventually supplant the other methods of administration of the hormone except possibly in mild cases. It has yielded by far the smoothest and most consistent results and from the patients' point of view will prove the most economical one.

#### SUMMARY AND CONCLUSIONS

Fifteen menopausal patients, including two surgical castrates, suffering from severe menopausal symptoms, were treated with testosterone propionate. In every case, the vasomotor phenomena, hot flushes, sweats, paresthesias, etc., were practically completely relieved. In addition, there was observed a rapid return to normal physical vigor along with an improvement in appetite and the general sense of well being. Genitourinary complaints of mild urgency and urinary frequency disappeared spontaneously during therapy. Three patients developed a peculiar tanning over the exposed portions of their body. In two patients with arthralgia in addition to the usual menopausal symptoms, estradiol dipropionate was alternated with testosterone propionate with complete relief.

The individual dose given by injection was 5 mg. of testosterone propionate. Injections were given subcutaneously two to three times a week and the interval lengthened with clinical improvement. With control of symptoms, oral therapy was instituted. This consisted of the daily administration of 5 to 10 mg. of testosterone propionate combined with bile salts.

The most satisfactory method of administration, from all viewpoints, has been the subcutaneous implantation of pellets of crystalline testosterone propionate totaling approximately 25 mg.

The testosterone propionate used in this study was supplied by the Ciba Pharmaceutical Products, Inc., under the trade name of "Perandren—Ciba."

The authors acknowledge their indebtedness for the preparation of the pellets to Dr. Gerson Biskind, of the Department of Pathology, Johns Hopkins University.

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The most important findings were numerous glandular structures which occupied the submucosa and branched toward the muscle coat. They were present also in the muscle, more in the internal than in the external layers. Nowhere did they reach the subserosa. They were lined by a single layer of columnar, partly ciliated, epithelium. The epithelium rested on a basement membrane. Some of the glandular structures were cystic. The epithelium of these cystic glands was flat or cuboidal, in some places cylindrical. The lumen often contained well-preserved, or degenerated erythrocytes, cellular detritus, and amorphous matter. In a few, large accumulations of polymorphonuclear leucocytes were present. Some of the larger glands had papillary protrusions. Only traces of cytogenic tissue could be found around the glandular structures in the submucosa, while it was more abundant around the glands in the muscle coat. Brownish, granular pigment was situated near the glands, both between and within connective tissue cells. There was no new formation of muscle, nor was the fibrous tissue increased.



Fig. 3.

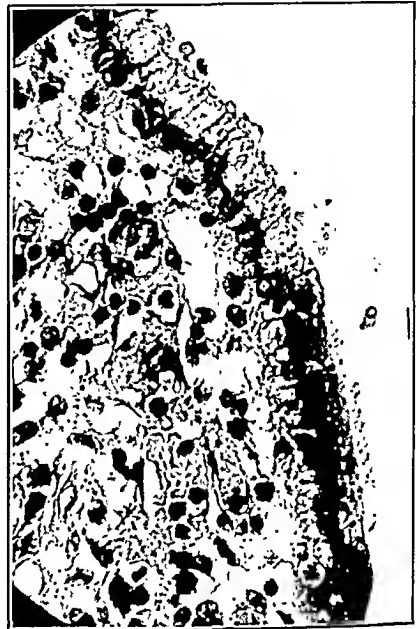


Fig. 4.

Fig. 3.—The transitional epithelium of the bladder mucosa is continuous with characteristic mucinous epithelium.

Fig. 4.—Ciliated epithelium and mucinous epithelium touching each other in one of the endometrioid glands.

In one area, in the center of the lesion, the surface epithelium reached particularly far into the submucosa, forming thus deep crypts, and the nests of Brunns were numerous and large. Here the glands opened into the crypts or into the cystic nests. The transitional surface epithelium was continuous with the columnar epithelium of the glands. The transition between the two types was rather sudden. In one ramification, the transitional epithelium changed into characteristic mucous epithelium which gave a positive intracellular mucicarmine stain. In another ramification, near the muscle coat and away from the surface, the continuity of the cylindrical epithelium was interrupted by the presence of mucous epithelium for a short distance.

*Diagnosis.*—Internal endometriosis of the urinary bladder.

#### COMMENT

R. Meyer has distinguished three types of endometriosis of the bladder:

1. Internal, originating probably from bladder epithelium.

to about 1.5 cm. from the right ureteral orifice. It was covered by a thickened mucosa. The trigone was normal.

*Gross Specimen.*—Ellipsoid specimen 3.5 by 3.5 by 2.5. Part of the surface appeared charred. On the surface a square of 3 cm. was formed by deep red bladder mucosa in which three dark brownish red spots, about 6 mm. in diameter, were situated. On bisecting, thin brownish fluid, suggestive of altered blood, came out. The cut surface looked grayish, with streaked markings. There were, notably near the periphery, a few small indistinct cavities from which the fluid exuded.

*Microscopic Description.*—The tumor was bisected at right angle to the bladder surface, one slice 1 mm. thick cut in serial sections, the rest at levels. Every tenth slide was stained. The stains used were hematoxylin-eosin, v. Gieson, elastica and mucicarmin.



Fig. 1.



Fig. 2.

Figs. 1 to 4.—The photomicrographs represent small portions of the endometrioid structures within the bladder wall.

Fig. 1.—The stroma has the characteristics of cytogenic tissue. The epithelium is cylindrical.

Fig. 2.—The stratified epithelium of the bladder surface is continuous with the single layered cylindrical epithelium of the gland. The aspect of the stroma is somewhat altered by edema.

The bladder epithelium extended with deep folds into the submucous layer. It was somewhat thickened. Many nests of Brunn were seen. Some of them, when followed in serial sections, appeared separated entirely from the surface epithelium. Others were continuous with it and represented the deepest parts of the folds. They were in part solid with occasional intraepithelial vacuoles, in part they had a lumen and were somewhat glandlike with their inner epithelial layer formed by cylindrical cells. The mucin reaction in these cells was negative. No secretion was found in the lumina. Some of them communicated with the lumen of the bladder, others had no demonstrable opening.

The submucous layer was highly edematous and inflamed. In one area the surface epithelium was entirely missing (site of biopsy).

The muscle coat was thick, but otherwise not remarkable. There was no evidence of new formation of muscle. The edema and inflammation extended into the internal muscle layer. In the subserosa occasional inconspicuous accumulations of lymphocytes were seen. The serosal cells were poorly preserved.

in one case, observed decidual reaction in the endometrial structures. In most cases, however, the only anatomic sign which could be referred to cyclic change is the presence of old and fresh blood.

Particularly impressive are the clinical observations of Mueller who was able to follow by serial cystoscopic examinations, the effect of pregnancy, x-ray, and hormone treatment upon the endometriosis.

These facts are definitely in favor of a dependence upon hormonal stimuli which most probably are ovarian. But there is no evidence, whatsoever, that endometriosis is caused by the action of hormones. Endometriosis might very well originate in an entirely different way and still come under hormonal influence secondarily. One cannot ignore the fact that, in many cases, the onset apparently follows mechanical trauma as operation, childbirth, curettage or some inflammatory condition in the pelvis or in the abdomen. In the case described by Plaut, a simple appendectomy only had been performed. It is difficult to imagine that this may have caused a hormonal imbalance. Even less conceivable, in such a case, is an implantation of endometrium.

For the cases of internal endometriosis of the urinary bladder, I would rather think that mechanical or inflammatory stimuli cause multipotent cells of the bladder epithelium to differentiate and that perhaps the direction in which they develop is influenced by hormones.

#### SUMMARY

The origin of the endometrial structures from the bladder epithelium is demonstrated in a case of internal endometriosis of the bladder.

The causative role of ovarian hormones in the genesis of endometriosis of the bladder is unproved. Once established, however, endometriosis is functionally connected with the ovary.

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Synephias: Spinal Anesthesia With Percaine for Cesarean Section, *Bull. Sec. d'obst. et de gynéc.* 28: 137, 1939.

In the Strasbourg Maternity, 67 cesarean sections were performed under spinal anesthesia. No serious complications were observed. This anesthetic was employed in spite of its well-known dangers because it preserves satisfactory uterine contractility, diminishes bleeding during operation, prevents postoperative atony, and is harmless to the child.

Local anesthesia is excellent, but it takes much more time and proves painful in women who suffer violent uterine contractions. Furthermore, local anesthesia is difficult to carry out when performing a cervical cesarean section with exteriorization of the uterus.

2. External, originating from serosal cells.
3. Collision, resulting from the combination of 1 and 2.

It is evident from the literature that most of the cases belong to Group 2. Regardless of the mechanism involved, whether there be implantation (Sampson), penetration (Haselhorst), or metaplasia, all these cases have one principal characteristic in common: the bladder is invaded from without by the endometrioid structures. Therefore, these cases must be considered as external endometriosis of the bladder.

Regarding internal endometriosis of the bladder (Group 1), the various authors are not in accord as to the criteria for establishing such an entity. Erle lists 21 cases out of 30 as "primary," Weijtlandt 3 out of 35. According to Stoeckel there are no cases of true internal endometriosis of the bladder at all. Mark expresses himself in similar fashion. Adams considers as "primary" only those cases in which there is no continuity with the sex organ and no peritoneal involvement, and in which previous operations have not caused a trauma to the bladder. The fact that, in many cases of "primary" endometriosis, the process starts evidently from without detracts from the usefulness of this term. It is much more accurate to continue the distinction of external and internal endometriosis. The latter term then would include those cases in which the origin can be traced to the bladder epithelium. It must, however, be kept in mind that the endometrioid structures may penetrate up to the bladder epithelium in cases of external endometriosis as well. The direction in which the glands ramify may then be helpful for a correct interpretation.

It seems surprising at first that endometrioid structures should arise in the bladder epithelium. Some authors as Erle, Oehlecker, Mueller and Frommolt thought that undifferentiated coelomic cells, or some other dysontogenetic rests in the bladder, gave rise to the endometriosis. The bladder, in fact, in the embryo, is lined originally by a single layer of cylindrical epithelium. This epithelium assumes its definite appearance only in embryos of 55 to 60 mm. length. On the other hand, the presence of glands in the normal bladder is not generally admitted. Outside the trigone where sometimes aberrant urethral glands may be found, glandular structures are not considered a normal finding, although Moellendorf, Lendorf, and others have described rudimentary glands in the bladder.

It is well known, however, that the bladder epithelium may form glands under pathologic conditions. The transformation of the epithelial nests of Brunn into glands has been shown recently by Patch and Rhea (cystitis glandularis). Nests of Brunn and gland formation are usually but not exclusively found in the inflamed bladder (Putschar).

Another proof for the potentialities inherent to the bladder epithelium is the formation of mucous epithelium. It has been found in chronic cystitis and particularly in exstrophy of bladder. Mucus-producing adenocarcinoma of the bladder has also been observed occasionally (Hueckel). Homma, Mueller, and Frommolt described mucous epithelium in their cases of endometriosis of the bladder. According to Homma, it is due to a metaplasia of the bladder epithelium. Mueller and Frommolt considered it as evidence of a dysontogenetic origin and thought that it was derived from aberrant rests of the primary gut.

True internal endometriosis of the bladder is rare. Only the cases of Mueller (1927, Case 1), Frommolt (1929, Case 1), Oehlecker (1930) can be considered as true internal endometriosis of the bladder. A probable case of internal endometriosis is that of Erle. There is no microscopic description but the illustration is highly suggestive.

In other cases (Weijtlandt and Reynolds) no biopsy was taken and therefore no conclusive judgment is possible. It is only by microscopic evidence that we can decide whether we are dealing with internal or external endometriosis.

Pathogenesis: It is evident from the cyclic character of symptoms and the cyclic change in size and appearance which can be observed with the cystoscope, that these structures are under hormonal and especially under ovarian influence. Phillips described different functional pictures in two subsequent biopsies. R. Meyer,

## SUMMARY OF CASES IN RECENT LITERATURE

AUTHOR	YEAR	AGE	GRAVIDA	DURATION OF PREGNANCY		CASE FINDINGS AND REMARKS
				EXTRA-UTERINE	INTRA-UTERINE	
Clarke	1934	27	ii	--	8 weeks	Right tubal pregnancy ruptured. Salpingo-oophorectomy. Patient recovered.
Clarke	1936	29	i	2 mo.	Term	Right tubal pregnancy ruptured. Partial salpingectomy. Patient recovered. Living child.
Neumann	1935	20	i	2 mo.?	2 mo.?	Left tubal pregnancy ruptured. Partial salpingectomy. Patient recovered.
Neumann	1935	34	vii	2.5 mo.	2.5 mo.	Left ovarian pregnancy ruptured. Oophorectomy. Patient recovered.
Neumann	1936	32	i	?	6 mo.	Intrauterine abortion. Left tube and ovary removed. Patient recovered.
Schürger	1935	--	--	2+ mo.	2+ mo.	Left tubal pregnancy ruptured. Salpingectomy. Patient recovered.
Rainey and Shera	1936	37	ii	3 mo.	2.5 mo.	Twin extrauterine pregnancy. Intrauterine pregnancy expelled at 2½ mo. Patient recovered.
Sertā	1937	40	iii	3 mo.	2 mo.	Right tubal pregnancy ruptured. Salpingectomy. Patient recovered.
Huber	1936	31	v	2.5 mo.	2.5 mo.	Ruptured left tubal pregnancy. Hysterectomy and bilateral salpingectomy. Patient recovered.
Bondurant	1937	34	vii	Term	Term	Extrauterine child recovered. Intrauterine child died on fifth day. Patient recovered.
Figueroa	1937	32	i	2 mo.	2 mo.	Ruptured left tubal pregnancy. Salpingectomy. Patient recovered.
Moudrý and Tachezy	1937	22	--	5 weeks	8 mo. Wt., 2,100 gm.	Ruptured left tubal pregnancy. Salpingectomy. Patient recovered. Child hydrocephalus, died 1 hour after birth.
Moudrý and Tachezy	1938	29	ii	2 mo.	2 mo.	Ruptured left tubal pregnancy. Salpingectomy. Intra interrupted artificially. Patient recovered.
Marten and Meyer	1937	26	ii	6 weeks	2 mo.	Ruptured left tubal pregnancy. Salpingectomy. Hysterectomy. Removal of fetus. Patient recovered.

# COMBINED EXTRA- AND INTRAUTERINE PREGNANCY\*

DAVID B. LUDWIG, M.D., PITTSBURGH, PA.

THE co-existence of intra- and extrauterine pregnancy is comparatively rare and sufficiently interesting to have been the subject of some excellent reviews by observers in this and other countries.

Combined pregnancy is to be distinguished from compound pregnancy, as in the former the intra- and extrauterine pregnancy occurs simultaneously, and in compound pregnancy the intrauterine pregnancy is superimposed on a previously existing ectopic pregnancy which has terminated in lithopedion formation.

Bland<sup>1</sup> in 1933 quoted authors who had collected 183 cases of compound pregnancy from 1582 to 1926, summarized 13 cases recorded to 1933, and reported one of his own, making a total of 197 cases. Mathieu<sup>10</sup> reviewed the literature from 1933 to 1937, collected 32 additional cases, including a personal one which totals 229.

There has been considerable variance in the number of cases of combined pregnancy reviewed by equally exacting observers due to difference of opinion as to the authenticity of some cases.

The publication of Gemmel and Murray's<sup>7</sup> exhaustive study in 1933, summarizes 217 cases from Duverney's case in 1708 to the end of 1931. Mathieu added 19 cases from 1928 to 1931 which he failed to find in the study of Gemmel and Murray. Mathieu's study through 1936 has added 57 cases. These combined with the 217 assembled by Gemmel and Murray make a total of 274 recorded cases to the end of 1936.

Novak<sup>13</sup> in 1925 reported 32 cases collected from the literature from 1913 to 1925, including 2 cases of his own. These added to the 244 cases assembled by Neugebauer (quoted by Novak<sup>13</sup>) from 1708 to 1913, bring the total to 276, and with 57 cases reviewed by Mathieu, total 333 through 1936.

I have reviewed 17 cases in the recent literature and am reporting 3 original cases which makes a total of 353 cases through 1938.

It is interesting to note that in 20 cases reported all mothers recovered. There were four pregnancies came to term (three intrauterine and one extrauterine) culminating in living children. One intrauterine pregnancy terminated at eight months, another continued through 6.5 months with the probability of having continued to term.

## AUTHOR'S CASES

CASE 1.—Mrs. H. I., colored, aged 25, was admitted to the Allegheny General Hospital Dec. 19, 1935. Her last menstrual period began September 30, being seven days late. Slight spotting of blood began November 10 and continued to the present time. On November 25 the patient experienced a severe attack of cramplike pain in both sides of the lower abdomen. This was followed by intermittent attacks of pain culminating in a severe attack on December 18. Her menstrual periods had always been regular. She had one miscarriage five years ago and has a child three years of age.

*Physical Examination.*—The patient was fairly well developed, rather thin and appeared very ill. Her abdomen was much distended with some rigidity of the left lower abdomen. The blood count showed red blood cells 3,450,000, white blood cells 24,800, hemoglobin 65. The temperature upon admission was 96.6° F., pulse 120, and blood pressure 80/42. Vaginal examination Dec. 19, 1935, revealed a softened and enlarged uterus in a forward position. A soft tumor mass was located posterior and to the left of the cervix. Diagnosis: Ruptured ectopic pregnancy.

*Operation* was performed Dec. 20, 1935. The left tube and ovary, the ectopic mass, and the blood (over a quart and mostly clotted) were removed. Due to persistent hemorrhage from the fundus of the uterus just beyond the left broad ligament attachment, a supravaginal hysterectomy was done. A blood transfusion of 650 c.c. was administered during the operation and dextrose and saline immediately

\*Reported at a regular meeting of the Pittsburgh Obstetrical and Gynecological Society, Pittsburgh, Pa., April 3, 1939.



A report of her continued pregnancy and delivery was not secured as she moved from this neighborhood.

*Laboratory Report.*—Section of blood clot from the lumen of the tube showed fibrin, red blood cells and placental villi with some lymphocytes in the tubal wall.

**CASE 3.**—Mrs. M. K., white, aged twenty-four years, was admitted to the Allegheny General Hospital Oct. 11, 1938. A few hours before admission she was seized with a severe pain in the lower abdomen and fainted. She experienced referred pain in the upper abdomen and later in the chest and shoulders, more marked in the right shoulder. There was a history of a miscarriage about Aug. 1, 1938. She bled almost every day from August 10 until a few days ago. Aug. 17, 1938, she was seized with a sharp pain in the lower right abdomen and was admitted to a hospital in the vicinity of Pittsburgh, remaining for seven days. The attacks of pain continued, recurred weekly to the present time. She has lost several pounds in weight and has grown progressively weaker. Her menstrual periods have always been irregular. She had a child one year ago and a miscarriage five years ago.

*Physical Examination.*—The patient was emaciated, pale grayish color, semiconscious. There was a mass which extended to the umbilicus, uniform in outline, filling almost the entire lower abdominal cavity. The contour of the abdomen resembled an intrauterine pregnancy. There was rigidity and marked tenderness of the lower abdomen and much distention of the upper abdomen. No vaginal examination was made. **Diagnosis:** Ruptured ectopic pregnancy with the possibility of an abdominal pregnancy. The blood count showed red blood cells 1,340,000, white blood cells 16,750, hemoglobin 40. The pulse ranged between 120 and 140, scarcely perceptible at times, blood pressure systolic 62, diastolic not determined.

*Operation* was performed at 1 A.M., October 12. Curettage showed thickened endometrium and placental tissue. Laparotomy revealed an abdominal pregnancy; the fetus was removed and the cord ligated. A portion of the placenta had become detached and was partially necrotic. The entire placental mass was removed. No active bleeding followed. There were over 2 quarts of blood, mostly fluid, in the pelvic and abdominal cavities, this being the greatest amount of blood the author has seen in any patient who has survived.

The fetus and some amniotic fluid were within the sac. The placental mass had been attached to the uterus, cecum, broad ligament, pelvic and abdominal walls, and portions of the small intestine. The abdominal pregnancy had progressed to a little over four months. The uterus was the size of a 2.5 months' pregnancy, very soft, friable, and but partially movable. The patient was given a transfusion of 1100 c.c. of blood during the operation.

On the second day following operation, the patient expelled some tissue from the uterus. Microscopic sections of this tissue showed it to contain decidual tissue and chorionic villi. **Diagnosis:** Infected placental tissue. Her convalescence was quite uneventful after the first twenty-four hours, and she was discharged fourteen days after operation.

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## SUMMARY OF CASES IN RECENT LITERATURE—CONT'D

AUTHOR	YEAR	AGE	GRAVIDA	DURATION OF PREGNANCY		CASE FINDINGS AND REMARKS
				EXTRA-UTERINE	INTRA-UTERINE	
Dolan	1937	28	i	2.5 mo.	Term	Ruptured left tubal pregnancy. Salpingo-oophorectomy. Normal child spontaneous. Patient recovered.
Sugasti	1938	27	ii	2+ mo.	3 mo.	Ruptured right tubal pregnancy. Salpingectomy. Intra interrupted artificially. Patient recovered.
Davydov	----	31	i	6 weeks	2.5 mo.	Ruptured right tubal pregnancy. Salpingectomy. Intra interrupted artificially. Patient recovered.
Ludwig	1935	25	ii	6 weeks	3 mo.	Ruptured left tubal pregnancy. Salpingo-oophorectomy. Hysterectomy. Patient recovered.
Ludwig	1935	31	viii	7 weeks	6.5 mo.	Ruptured right tubal pregnancy. Salpingo-oophorectomy. Observed to 6½ mo. pregnancy. Patient recovered.
Ludwig	1938	24	ii	4.5 mo.	2 mo.	Abdominal pregnancy. Right salpingo-oophorectomy. Patient recovered.

after. Convalescence was rather stormy the first seventy-two hours but very satisfactory thereafter. The patient left the hospital fourteen days after operation.

*Laboratory Report.*—The uterus measured 7 by 6 by 5 cm. and was quite soft. At the opening in the amputated cervix there was bulging of fetal membranes. The sac was filled with amniotic fluid and contained a fetus measuring 6 cm. in length. The left tube contained some placental tissue and a small embryo (12 mm.) inclosed in a large blood clot.

CASE 2.—Mrs. M. B., white, aged 31 years, was admitted to the Columbia Hospital Dec. 25, 1935. Her chief complaint was pain in the entire lower abdomen which began two weeks before admission, occurring intermittently and becoming progressively worse. Her menstrual periods had been regular. She had had 5 full-term pregnancies and 3 miscarriages. There had been no bleeding since her last menstrual period November 3.

*Physical Examination.*—The patient was well developed, rather obese, weighing 180 pounds. The abdomen was slightly distended with some rigidity of the lower abdomen. The blood count showed red blood cells 4,450,000, white blood cells 9,050, hemoglobin 90. The temperature upon admission was 98.6° F., pulse 90, blood pressure 130/80. *Pelvic examination:* The cervix was softened. There was a soft rounded mass posterior to the cervix which could not be definitely outlined on account of pain and tenderness. Following the administration of morphine, examination revealed an ectopic pregnancy.

At operation December 28 the right tube and ovary, the ectopic mass, and the blood were removed. The uterus was situated well forward, softened, and the size of a 2.5 months' pregnancy. An intrauterine pregnancy was considered. Convalescence was uneventful. The patient left the hospital fifteen days after operation. She was last seen April 30, 1936, at which time the pregnancy had advanced to 6.5 months.

the middle third. The right ovary was small and cystic. The right tube with the mass was removed and the abdominal wound was closed without drainage.

During convalescence she was given by transfusions, a total of 1,150 c.c. of citrated blood. She recovered and left the hospital on the twelfth day, having had normal temperature for five days.

Pathology report by E. Pund. "Bilateral simultaneous tubal pregnancy. Hemorrhagic dissociation of the chorionic sac in ampulla of right tube forming a mass 3 cm. in diameter. The villi are necrotic and the blood is degenerated. Ruptured and hemorrhagic pregnancy of ampulla of left tube forming a hemorrhagic mass 5 centimeters in diameter, with good preservation of the blood and villi. The sac has ruptured through the tube and is now enclosed partly in the omentum. Suppurative inflammation of the fimbriated end of this tube. Small corpus luteum of left ovary."

## NONTRAUMATIC, SPONTANEOUS RUPTURE OF UTERUS

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PATERSON, N. J.

*(From the Obstetric Service of St. Joseph's Hospital.)*

THIS is a presentation of a case of spontaneous rupture of the uterus, occurring between the seventh and eighth months of gestation, of an unusual type.

Mrs. May T., white, aged 29 years (gravida iv, para ii), was seen in the Prenatal Clinic of this Hospital on June 2, 1938. Past history included a mastoidectomy at ten years of age and a dilatation with curettage one year ago, following a miscarriage at two months of gestation. The length of her previous labors was not unusual. Her first delivery was assisted with low forceps; the second was entirely spontaneous. Physical examination on June 2, 1938, was essentially negative. The pelvic measurements were normal and prognosis as to labor was good. Urine and blood Wassermann were negative.

The patient was again seen in the clinic on July 2, 1938, and July 9 at which time she stated that during the preceding month she had had a discharge from both ears with associated headache and diplopia.

She did not return to the clinic until Sept. 22, 1938. At this visit nothing unusual was found. Diagnosis of position was right occiput posterior.

Eleven days after that visit (Oct. 3, 1938) she was brought to the maternity ward by automobile. On admission the admitting nurse noticed nothing unusual about the patient's condition; the fetal heart sounds were in the left lower quadrant, rate 140. At 9 P.M. the patient was seen by the interne on service. He obtained a history of onset of abdominal pains at 4 A.M. of the same day. These pains recurred every five to ten minutes throughout the day. However, the patient went about her daily routine, bothered only by occasional vomiting. At 6 P.M. her pains began to increase in severity until finally she decided to come to the hospital, arriving at 8:40 P.M. At no time had she had any sudden, severe or knife-like pain.

On examination the patient appeared rather pale, pulse was 96 and of good quality, respirations 24. Fetal heart sounds could not be heard by the interne at this time, nor could the nurse who had heard them ten minutes previously obtain them again.

The patient appeared fairly comfortable, complained of no acute distress except for some moderate abdominal pain which, however, was now present almost constantly. The entire abdomen was tender to pressure but was perfectly soft. No uterine contractions were felt. The fetal parts could be easily mapped out, position being left occiput anterior. Pelvic examination revealed the cervix to be soft and about 3 cm. dilated. There was no effacement. Membranes were intact: The head was engaged in the pelvis. No vaginal bleeding or discharge was present.

# SIMULTANEOUS BILATERAL TUBAL PREGNANCY

## REPORT OF CASE

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(From the Department of Obstetrics and Gynecology, University of Georgia School of Medicine)

ACCORDING to H. R. Fishback\* who has recently reviewed the literature, there are recorded 76 acceptable cases of bilateral simultaneous tubal pregnancy. His criteria include "description of the fetuses or any portion of them found, as well as of placental material." He presents the third case of simultaneous twin pregnancy in one tube and single pregnancy in the other tube.

Bilateral simultaneous tubal pregnancy must be considered to be a form of double ovum twin pregnancy as also pregnancy in the uterus simultaneously with an ectopic pregnancy, so-called heterotopic pregnancy. Of the two conditions this latter is apparently much more frequent since there are more than 300 cases reported.

*Case Report.*—L. M. W., colored female, 37 years of age, medium constitutional type, entered hospital Sept. 22, 1938. She was married seventeen years to the same husband. She had had 8 children, 7 of whom are living, aged 5 to 16 years. She gave a history of normal menstrual periods on June 1, July 1, and August 1. She began to bleed vaginally in the first week of September. Before she began to bleed she had bearing down pains in each side of lower abdomen simultaneously. The day following the onset of the pain she began to bleed dark blood, scanty, stopping and starting again and this continued until she was operated upon on September 22. The pain, she states, kept her awake for three weeks. She described it as rolling and cramplike and said that it extended up into her chest on both sides. During this time she fainted whenever she tried to stand. She gave a history of nausea and vomiting which began about the same time as the onset of the pain. She stated that urination caused burning and bowel movement increased her pain.

The physical examination revealed a fairly well-nourished, severely dehydrated markedly anemic negress. The abdomen was distended, and there was a shifting dullness, and marked tenderness over both quadrants. No edema of legs or vulva. Pelvic examination revealed a multiparous perineum and a dark bloody vaginal discharge. The uterus was freely mobile and slightly enlarged. There was a fixed and tender mass the size of an orange in the left adnexal region. Right side was free except for a mass the size and mobility of a normal ovary.

A diagnosis of ectopic pregnancy was made and colpotomy operation ordered, which was done immediately.

Laboratory findings previous to operation: White blood count, 11,000; red blood count, 1,500,000; Hg, 30 per cent; no malarial parasites; temperature, 99° F.; pulse, 80; respiration, 26; urine normal except acetone 2+.

Operation was done on Sept. 22, 1938. Under cyclopropane anesthesia a posterior colpotomy was done, merely making a hole in the posterior cul-de-sac where old dark blood was found; the incision was closed with catgut and a laparotomy operation performed with mesial suprapubic incision. The peritoneal cavity contained more than one quart of old, dark, fluid blood and an orange-sized mass was found in the left adnexal region matted together with the left tube, left ovary, and the omentum. The omentum was ligated and cut free. The left tube, left ovary, and the clot were removed en masse. The right tube contained a walnut-sized mass in

\*Fishback, H. R.: AM. J. OBST. & GYN. 37: 1035, 1939.

Note: The fetal heart was not heard at 9 P.M. after having been heard only ten minutes previously.

4. The tear of the uterine wall continued to extend as the uterus retracted downward over the amniotic sac and its contents. As the fundus passed by the fetal shoulders, release of the compression occurred with resulting hemorrhage into the abdomen, associated with the onset of acute symptoms of shock.

206 CARROLL STREET

## IMPROVED INSTRUMENT FOR ENDOMETRIAL BIOPSY\*

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THE instrument consists of a cannula about  $\frac{3}{16}$  of an inch in diameter and about 10 inches in length. The proximal end has attached a standard Luer hub. The distal 1 inch is slightly curved. The distal end is sealed and rounded. About  $\frac{1}{4}$  inch from the distal end on the convex aspect of the shaft a sharp tooth is cut. The convex surface of the shaft immediately below this tooth is cut away deeply for a distance of one inch (Fig. 1).

### TECHNIQUE

The cervix is exposed with a bivalve speculum. All secretions from the cervix and vagina are wiped away. The cervical canal, portio and vaginal mucosa are painted with tincture of iodine. The sterile biopsy cannula is introduced, with or without previous cervical dilatation, directly into the uterine cavity. A Sana-Lok syringe is attached to the hub. The plunger of the syringe is drawn back creating

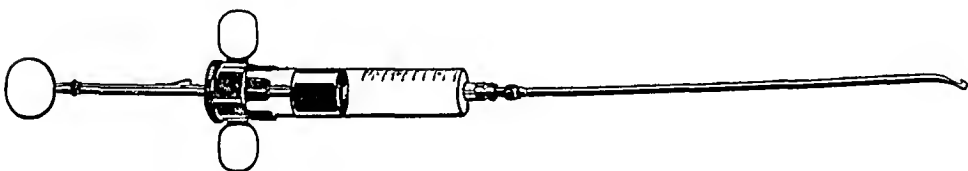


Fig. 1.—Endometrial biopsy cannula with Sana-Lok syringe attached.

suction. A device on the plunger maintains this suction automatically. Several aspects of the endometrial cavity are gently curetted without withdrawing the cannula. The continuous suction draws the fragments of tissue into the lumen of the cannula and syringe. Upon withdrawing the cannula a sucking noise is audible when the fenestrum of the instrument emerges from the external os. This demonstrates that the obturation at the cervix has been effective and continuous suction maintained in the uterine cavity. The tissue obtained is placed in a suitable solution for transmission to the laboratory.

The cannula here suggested has several advantages:

1. It is easily introduced.
2. The cutting edge and fenestrum on the convex aspects permit close apposition to the endometrium.
3. Satisfactory specimens are easily obtained without undue pressure.
4. Danger of traumatization or puncture of the uterus is eliminated.

151 WEST 77TH STREET

\*Instrument supplied by Research Department, Becton, Dickinson & Co.

At 10 P.M. (one hour and twenty minutes after admission) the patient suddenly went into shock, the skin and mucous membranes becoming absolutely blanched, pulse rapid, thready and barely perceptible. Her temperature fell to 95° F., and she became markedly dyspneic, restless, and irrational.

Treatment for shock was immediately instituted. Before the onset of active treatment the death of the patient appeared imminent. However, she picked up rapidly following onset of shock therapy. Color was regained to some extent; pulse was slower and stronger; dyspnea lessened and the patient became rational and cooperative again but was still somewhat restless. She stated that she felt very weak, still had constant abdominal pain and a sensation of numbness in her legs.

At about this time, 10:30 P.M., the abdomen was still perfectly soft. Fetal parts were easily and readily palpable, especially at the upper pole of the uterus in the right upper quadrant of the abdomen. Here the fetal parts (feet) seemed to be just beneath the abdominal wall with no interposing uterine wall present. There, however, appeared to be no uterine asymmetry.

A diagnosis of probable uterine rupture was made and laparotomy indicated. Unfortunately, considerable time was lost in attempting to secure a suitable donor compatible with the patient's type of blood. In the meantime, her condition became worse and she died at 1:30 A.M.

*Autopsy* revealed the following: "The peritoneal cavity is filled with approximately 3 liters of bloody fluid and large blood clots. Lying free in the abdominal cavity there is a fetus surrounded by an intact amniotic sac. The placenta is still attached to the posterior aspect of the sac and is partially extruded into the abdominal cavity. It can be traced distally into the uterus, which is ruptured at the fundus clear across cornu to cornu. The uterus encircles the neck of the fetus, the head in the uterine cavity being well down in the pelvis. The trunk and extremities lie free in the peritoneal cavity. The uterus is soft, flabby and but loosely applied to the neck of the fetus. The body of the uterus is enlarged to about five times normal size, apparently having retracted after rupture. There are no tumors, scars or other defects in the uterine wall."

*Anatomic Diagnosis.*—Rupture of fundus of uterus with expulsion of the fetus into the abdominal cavity; fatal intraperitoneal hemorrhage; seven and one-half months' pregnancy.

#### COMMENTS

This case presents the following unusual features:

1. The location of the rupture.
2. The period of gestation between the seventh and eighth months.
3. The absence of any history or physical findings of trauma or other external cause.
4. An adequate pelvis.
5. The unusually strong resistance of the amniotic sac which did not tear at the time of uterine rupture nor during the two vaginal and the frequent abdominal examinations.
6. The resistance of the patient. She was strong enough to go about during the day, come to the hospital in a car, walk into the ward, and then give a history herself of what occurred during the day even though, in all likelihood, her uterus had ruptured some time before admission.

The peculiar characteristics of this case may perhaps be explained on the basis of the autopsy findings, as follows:

1. The uterus apparently had a weakened muscular wall, possibly due to the dilatation and curettage performed about one year before this conception.
2. With the first uterine contractions the weakened section of the fundus probably gave way. The amniotic sac and its contents entered the rent, at once stopping any bleeding by compression—acting as a tampon.
3. The laceration of the uterine wall continued to increase in size. The walls of the uterus slipped down over the amniotic sac and its contents until about 9 P.M. when the laceration reached the point of placental attachment.

This cooperation has been shown in various ways: In 10 states the Committee on Maternal Welfare and the State Health Department work jointly, acting in an advisory capacity to the projects that are carried on by the departments with the cooperation of the physicians, developing maternal mortality studies in eleven states, and prenatal and postnatal clinics in almost all states. In addition refresher courses of postgraduate study for physicians have been provided where the lecturers have been members of the State Societies and the expenses were usually defrayed by the State Department of Health in 24 states.

Information gleaned from these questionnaires shows that in every state maternal welfare is receiving the attention it deserves from organized health workers. It shows, in the opinion of the Public Health officials of more than half the states, that Organized Medicine through State and County Medical Societies has been a factor in reducing mortality rates and that their continued efforts will result in still greater improvement. It shows that there has been splendid cooperation between Public Health officials and private physicians and that this has been evidenced in joint effort in such ventures as maternal mortality studies, prenatal clinics, postgraduate lectures to physicians, and many other activities.

Replies to the questionnaires addressed to State Medical Societies showed that in 41 states (83 per cent of the total) maternal welfare committees are organized and working. Most of these committees have been formed within the last eight years. A few are older (Connecticut, 1927, Tennessee and Alabama State Societies organized in 1925). Much older is the Committee of the Maryland Society dating back to 1903, while the granddaddy of them all is in Kentucky where the State Medical Society organized a Committee on Maternal Health in 1851, "believe it or not!"

These committees have been advisory to State Health Departments, have engaged in state-wide maternal mortality studies, have given lectures in postgraduate courses in obstetrics to physicians, have been instrumental in regulation of hospitals including requiring consultation in complicated obstetric cases, have circularized the medical profession with literature on better maternal care. In addition, they have carried on lay education by articles for the press, by giving radio talks and lectures before lay groups.

In addition to State Health Departments and State and County Medical Societies, there are, of course, organizations, national in scope, of extreme importance to the maternal welfare cause: The American Committee on Maternal Welfare (1919), an organization made up of representatives of many national and regional Obstetric and Pediatric Societies; The American Public Health Association; and The Federal Children's Bureau of the United States Department of Labor. First, The American Committee has carried on a program "by furthering the practice of safe and sane obstetrics and by stressing the importance of improved antepartum, intrapartum, post-partum, and postnatal care in the interest of the mother and her offspring and the community." It promoted the organization of regional, state and local maternal welfare committees among medical societies from its very inception. It has sponsored the publication of pamphlets on standards of prenatal care, standards of intranatal or delivery care, standards of postnatal care. It sponsored through a special committee the production of an educational film, "The Birth of a Baby," which has been shown as a feature film in about half of the states to probably millions of people. Second, The American College of Surgeons has formulated minimum standards for obstetric departments in hospitals, the fulfillment of which is required of all ACS approved hospitals. Third, The American Hospital Association has required isolation of the obstetric departments in all general hospitals and a competent staff with power to enforce consultation in complicated cases. Fourth, The Maternity Center Association of New York, now national in scope, has for ten years conducted a continuous educational campaign for better care for the parturient. Two hundred thousand people visited its exhibit at the Century of Progress in Chicago, and its display at the New York World's Fair is attracting even more attention. It annually expends eighty-five to ninety thousand dollars in its propaganda work. Fifth, the Welfare cause owes much to a life insurance company and to a

# Department of Maternal Welfare

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CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

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## MATERNAL WELFARE, WHAT ARE ITS FRUITS?\*

JAMES KNIGHT QUIGLEY, M.D., F.A.C.S., ROCHESTER, N. Y.

PERHAPS a better title for this presentation might be, "Are the Efforts Expended in Maternal Welfare Work Justified by the Results?" Maternal welfare falls into the domain of preventive medicine, practically all the planned, constructive work has been done within the past twenty years and most of it within the last decade.

The decline in the obstetric death rate in the United States within the last five years has been quite general in extent and appreciable in amount, therefore it should be of interest to attempt a correlation of this improvement with maternal welfare work. To this end, two questionnaires were sent, one to State Departments of Health and the second to State Medical Societies. Both groups cooperated splendidly and the number of replies and the information furnished were very gratifying. Of the 49 questionnaires sent to State Health Departments, 44 were returned either through the Commissioner of Health or the Director of the Department of Maternity and Child Hygiene and 47 out of 49 State Medical Societies. Information was obtained then from one or both sources from 48 of the 49 states. Let us first consider the replies of Health officials.

It was found that every State Department of Health has a Division of Maternal and Child Health and that in at least eight states these special departments have been engaged in constructive work in maternal welfare for twenty years or more and that in at least fourteen states the Health Departments were alive to the necessity for this work before the passage of Federal legislation. Parenthetically, it might be said that in some of these states action was a result of the Sheppard Townner Act of 1921.

The nature and scope of the work of these Departments of Maternal and Child Health can be briefly tabulated as follows: (1) Organizing and conducting prenatal clinics, including case finding. (2) Lay education, emphasizing the necessity for early prenatal care by radio lectures, posters, and moving pictures, prenatal letters for pregnant women, classes in motherhood, and booklets for the expectant mother. (3) Postgraduate courses for physicians; refresher courses. (4) Demonstration delivery services furnishing nursing care. (5) Consultation service. (6) Establishment of small maternity homes in rural areas. (7) Licensure of maternity hospitals and homes. (8) Public Health Nursing services for prenatal and delivery service. (9) Education, licensing, and regulation of midwives, particularly in the Southern States.

Health officials of all the states where State and County Medical Societies had organized committees on maternal welfare agreed that the reduction in maternal mortality was due in a measure to the work of these committees and with two exceptions said that they had had the enthusiastic cooperation of organized medicine through their committees. I wish to quote here from Dr. J. A. Milne, Director, Maternal and Child Health of the Mississippi State Board of Health, "It is only through the approval of Health Department policies by Maternal Welfare Committees of State and County Medical Societies . . . that an effective program in maternal hygiene can be promoted and aimed toward reducing maternal mortality."

\*Read at the Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 7 to 9, 1939.



What has been the cause of this gratifying lessening of the risk incident to childbirth, the estimated saving of 1,746 lives in 1937 over 1936? One word will pretty well answer this question—education. Public Health work in general is one of education, and this certainly applies to the field of maternal welfare. Education includes better undergraduate teaching in the Medical School; post-graduate education for physicians as given in the refresher courses in Obstetrics; education of hospital authorities to furnish proper institutional care for parturients, separating the obstetric housing and personnel from the other departments in a general hospital, and requiring consultation in complicated cases; educating of midwives, particularly in the southern states where they are still a large factor; and, above all, educating of the public—lay education through literature such as mothers' guides, education through the channels of the Parent-Teachers' Association and other groups, education by radio, by exhibits such as that at the World's Fair, forever stressing the need to report to a physician or clinic early in pregnancy.

An increase in hospital deliveries has accompanied this decline in death rate; the figure for the entire country in 1937 was 45 per cent. We have heard much as to the dangers of births in American hospitals, the greater part of which should be forgotten, for it is not true. I believe that with better regulations of hospitals taking obstetric cases, with the requirement of consultation in complicated cases,

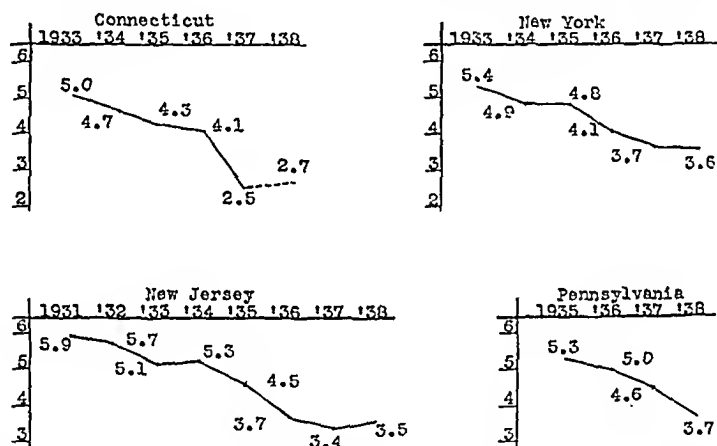


Fig. 2.—Trend of maternal mortality in four states where considerable maternal welfare work has been done.

the hospital is and will be increasingly a factor in lessening the rate. However, the fact that artificial delivery is much easier is probably the worst indictment chargeable to delivery in a hospital. Dr. Colebrook of London, in a lecture on the control of puerperal fever, favors the maternity hospital, for in four years in hospitals only one patient in 700 had hemolytic streptococcus infection, while in domiciliary midwifery the proportion for this period was one to 115. I wish to quote from *An Obstetric Audit* by Scott Runnels, Secretary of the Hospital Obstetric Society of Ohio, "The importance of the hospital as the major factor in the control of maternal mortality is further evidenced by the great increase that has occurred in the hospitalization of the obstetric patient. . . . The percentage of births that occur in hospitals comes closest to indicating the position a locality will have in its maternal mortality standing. One-fourth of the states have more than 60 per cent of their births in hospitals, while the last fourth have less than 25 per cent in hospitals. Comparing the percentage of hospitalization in the various states for 1937 with the maternal mortality rates in the same states for the same year, one makes the striking discovery that twenty-two states fall in the same category on the two charts and that only three states show any marked deviation. The extent of this parallelism in the two charts is the strongest possible argument in establishing the fact that the extent of hospitalization determines the incidence of maternal mortality."

pharmaceutical concern which devoted whole page publicity in many magazines in urging women to report early for obstetric care. Sixth, Public Health Nursing Service. In this field during the year 1938 there were:

Patients admitted to antepartum nursing service	236,324
Field and office visits to and by patients antepartum	671,790
Patients given nursing service at delivery	19,222
Patients admitted to postpartum nursing service	162,782
Nursing visits to patients postpartum	522,406

The American Board of Obstetrics and Gynecology has raised and unified the standards for specialization during the past ten years.

Having marshalled this extensive array of effort, we might now quite properly ask, how much has the maternal death rate declined? What are the causes of the decline? And can this improvement be correlated in general or in certain communities to maternal welfare efforts?

The trend of maternal mortality in the United States is shown by the graph in Fig. 1.

Between 1930 and 1936, there was a decline from 6.7 to 5.7 per 1,000, or 14.9 per cent. Between 1936 and 1938, there was a decline from 5.7 to 4.2 per 1,000, or 24 per cent in two years (estimated). The rate for 1938 is a provisional one and conservative estimate places it lower than this figure. Between 1930 and 1936 there

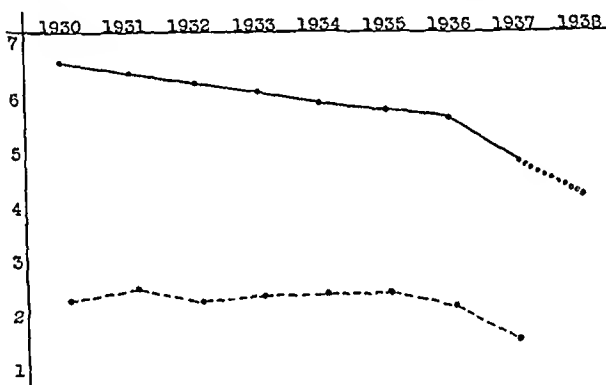


Fig. 1.—Solid line represents deaths per 1,000 births, all causes. Broken line represents deaths from infection, including septic abortion.

was a decline to 57 per 10,000, 14.9 per cent, or 3 per cent per year. From 1936 to 1937, however, the rate dropped to 49 per 10,000, a fall of 14 per cent in one year, almost equalling the total decline of the five previous years, and it is estimated that from 1937 to 1938 there will be at least a 10 per cent decline (with a provisional estimate of 16 per cent), a total of 24 per cent for two years.

If we break down the national maternal mortality figures, we will find that the deaths from toxemia, eclampsia, and allied conditions have not shown a marked drop in the last five years, the greatest gain having been made prior to five years ago. However, a very encouraging finding is that during 1936 and 1937 there was a marked decline in deaths due to infection, including septic abortion.

In the 13 largest cities of the United States the maternal mortality rate has shown a marked recession in the ten years from 1928 to 1937 and in three of these cities, Baltimore, Detroit, and Pittsburgh, the reduction was 50 per cent or better.

States where Maternal Welfare has been established longest and where the work has been very active show the greatest gains. For instance, in New York from 1933 to 1938 the rate fell from 5.4 to 3.6; in Connecticut during the same six years, from 5 to 2.7; in New Jersey from 1931 to 1938, from 5.9 to 3.5 per 1,000; in Pennsylvania from 1935 to 1938, from 5.3 to 3.7, an improvement of approximately 33½ per cent in each state.

tions; also complete prenatal care, adequate facilities for home and institutional care. It will be impossible for many years to come to hospitalize all women who are having babies, even if this were advisable, but certainly hospital facilities should be available for those who need them and for the many cases that cannot be taken care of properly in their homes.

We must have proper post-partum care and every community should have adequate facilities where such care can be continued. The information that is acquired in prenatal care must be used in the delivery and aftercare of the patient. The completeness and continuity with competency of the care are vital factors.

DR. N. F. PAXSON, PHILADELPHIA, PA.—In Philadelphia our own Maternal Welfare Committee, whose findings tend only to confirm what Dr. Quigley has already shown, was started in 1931 under the leadership of Dr. Phillip W. Williams. Our mortality rate has been reduced from 5.6 to 2.8 per thousand for the first six months of 1939, and we believe it can be reduced still further.

When the committee first met there was a wide diversification in methods of handling obstetric abnormalities, but there is now a tendency to pool the knowledge and to accept the best treatment offered. For instance, in septic abortion methods were in vogue which varied from immediate curettage to the most conservative treatment, but there is now a more or less standard method universally agreed upon.

Another point of great value is the formation of a courtesy staff rule which has been adopted by every hospital in Philadelphia. Not alone the obstetricians but also the family physicians have improved their work.

DR. ARTHUR W. BINGHAM, EAST ORANGE, N. J.—In New Jersey the Chairman of the Committee on Maternal Welfare of the Medical Society is also Chief Advisory Obstetrician of the State Department of Health. Each county has a field physician who is a part time man paid by the State Department of Health. He is the contact man between the State and County Maternal Welfare Committees, the State Department of Health and the physicians of the county. His duty is to stimulate among the physicians in his county interest in and familiarity with modern educational and preventive maternal welfare and child health practices.

New Jersey has an advantage in being one of the smaller states with only 21 counties and about 56,000 live births annually. It also has a disadvantage in having a higher percentage of colored births than any other northern state.

DR. ROBERT E. SEIBELS, COLUMBIA, S. C.—The Committee on Maternal Welfare of the South Carolina Medical Association was formed in the spring of 1934 and is the offspring of the series of refresher courses given by Dr. J. R. McCord when he stimulated our interest in the problem. Our efforts have been rewarded by some success, as in the five years there has been a reduction in maternal mortality of nearly 25 per cent. The lowering of the rate has been continuous and has been too widespread to be considered accidental.

With us it is a very different story from that in Philadelphia and New Jersey: for example, only one-half of the deliveries in South Carolina are supervised by physicians, the other being by midwives. We attempt to train the midwife, but about the best we can do is to eliminate the aged and infirm, and the grossly unfit; the best of them are not midwives in a real sense of the word.

About 10 per cent of all the births are in the hospital and of these only 10 per cent are planned hospital deliveries, the others represent admissions of the seriously ill. Maternal Welfare with us is really a rural problem, and to meet it we have instituted a three-point program. Since 1935 we have conducted a survey of each death classed as puerperal by the Board of Health with an annual tabulated report to the State Association.

The hospitals for the most part have open staffs, and there are only a dozen physicians in the state with postgraduate obstetric training. Of the 42 hospitals in the state, we have succeeded in having 10 adopt our rules and regulations for the care of the obstetric patients. The adoption and carrying out of these rules, with the educational efforts directed to the physicians, constitute the two educational features of our program.

## SUGGESTIONS FOR THE FUTURE

First, I wish to quote the conclusions of a paper on Maternal Welfare written by me in 1935. "Let us not become discouraged by the apparent hopelessness of the task. It is formidable, and yet even greater battles in Public Health have been won. Diphtheria, for instance, has been almost eliminated. In the last analysis the author believes that improvement will not be sudden or spectacular but will come only from continued effort, and chiefly in two ways: (1) education of women to seek prenatal care early; (2) in the practice of conservative, sane, clean obstetrics." And now, four years later, we are for the first time noting hopeful signs. This work should not be sporadic or spasmodic, but means continuous effort. Emphasis should be placed upon more refresher courses for doctors with clinical hospital postgraduate courses in hospitals, preferably under the auspices of medical schools; more Analysis (or Maternal Mortality) Committees; more County Committees on Maternal Welfare; lay education as to the dangers of abortion; continued lay education—"If pregnant, see your doctor early"; close cooperation between Public Health officials and Medical Societies in more states.

## CONCLUSIONS

1. After remaining stationary for many years, the maternal mortality rate throughout the United States has fallen considerably during the past five years. The American Committee on Maternal Welfare has for twenty years been urging doctors to lead in promoting better maternal care in their localities.

2. For at least ten years much maternal health work has been done by Public Health officials, by Organized Medicine, by Public Health Nurses, and by other agencies.

3. These two facts are not merely coincidental but are closely related.

4. The increasingly large number of deliveries in *approved* hospitals is a factor in a lower death rate.

5. The objectives of a maternal health program should be to reduce not only deaths, but morbidity. Good obstetric care should return a woman to a state of health as good as before her pregnancy, with a living, healthy child. Any plan which reduces mortality will coincidentally reduce morbidity.

6. The battle is not won but only begun. We must continue this work along lines already laid down and expand it.

26 SOUTH GOODMAN STREET

## DISCUSSION

DR. FRED L. ADAIR, CHICAGO, ILL.—The campaign for better prenatal care began about 1912 in Boston, in connection with the development of tentative and casual plans for prenatal care. About twenty years ago the American Committee on Maternal Welfare originated in the Society for the Prevention of Infant Mortality. Then we had the Shepard-Towner Act, with a great deal of discussion about mortality rates in this country compared with those in others. This aroused a great deal of antagonism, some contending that our results were as good as could be expected, while others thought they were not.

One of the epoch-making studies was done under the direction of Dr. DeNormandie, which included a study in 13 states for two years and 15 states for one year. This focused attention very sharply on these problems. Then there were the New York City studies under the auspices of the Commonwealth Fund, later the Philadelphia and other studies.

One of the major aims of the American Committee, since it began, was to stimulate the formation of County and State Maternal Welfare Committees in connection with the various state and county medical societies. This has led to the formation of state committees in practically all of the states, but there is still a lot for the state committees to do.

There are a few points that should be emphasized about maternal care. It must be complete and continuous; that is, every community must have facilities for taking proper care of the mothers and their offspring. This includes premarital examina-

number of women delivered in our city approaches 13,000 per year. It is estimated that about 9,000 of these are delivered either in private institutions or by private physicians. The remaining 4,000 cases are indigent and receive obstetric care from the Health Department of the District of Columbia. It is interesting to note that during the year 1937 there were registered at our Health Department prenatal clinics less than 700 patients. At the present time the registration has been increased to about 4,000; and so we feel that almost all the indigent maternity cases in the city have been contacted. This of course affords us some control over mortality and morbidity of the indigent population.

DR. JAMES R. McCORD, ATLANTA, GA.—There is probably more in the problem of maternal mortality than good obstetric care. You can take any map of maternal mortality rates and you find that most of the Southern states have high rates. Also, in general, the colored rates are nearly twice as high as the whites. You might immediately say that we are not doing good obstetric work in the South.

I live in a city of approximately one half million people, with a colored population of 150,000. We deliver about 2,200 colored women a year in our clinic in the municipal hospital. Our obstetric service is far from being a finished service but it is a conservative service. Our total operative incidence is 3.96 per cent which includes the packing of the vagina. Our forceps incidence for term and premature deliveries is 1.3 per cent; the cesarean incidence 0.46 per cent, and yet we have an uncorrected maternal mortality rate of 6.4 per 1,000 pregnancies. These women are getting good obstetric care and yet we have a tremendous mortality rate. Approximately 45 per cent of the women on our service are either illegitimately pregnant, the husband unemployed or on W.P.A.

With agriculture in the depths negroes all over the South are moving into the larger communities where they are badly housed and ill fed. Sepsis is the killer of colored women, and certainly on our service we can conscientiously say that it is in large measure not our fault. I do not mean in the least to deprecate good obstetric care, but I do believe that permanent lowering of maternal mortality must be accompanied by a proportionately rising economic level.

DR. QUIGLEY (closing).—Dr. Falls brought up the question of county committees. My feeling is that it is necessary that the larger states should be subdivided into districts of several counties each to facilitate supervision of the work. Committees of the smaller County Medical Societies have little idea as to what is expected of them unless an outlined program can be given them by the State Society Committee. In smaller states subdivision into districts is probably unnecessary.

Replying to Dr. DeNormandie, we have been rather fortunate in Rochester in that all hospitals have agreed to require consultation. The result is that practically all abnormalities, other than low forceps cases, must be seen by a consultant who must be an obstetrician and a staff member of some hospital in the city.

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Hoare, E. D.: The Case for Prophylaxis With Sulphanilamide and M. and B. 693, *Lancet* 1: 76, 1939.

It is possible to protect mice against an infection with hemolytic streptococci by prophylactic treatment with sulfanilamide or the related M. & B. 693. A high bactericidal power was demonstrated in the blood of uninfected human patients treated with sulfanilamide during the puerperium.

The prophylactic use of 1 gm. of sulfanilamide 3 times daily beginning at the onset of labor and continuing for three or four days is suggested. The author would limit its use to circumstances where special risk of infection with the hemolytic streptococcus is present, and he points out the undesirability of routine or indiscriminate use.

CARL P. HUBER.

Finally a limited program of birth control has been adopted because our surveys have established that 25 per cent of the maternal deaths occur among those who, by reason of previously existing chronic diseases, may be classed as temporarily, or permanently, unfit for pregnancy. There has been set up in each county health department the necessary organization to give contraceptive advice and supplies to those patients who have a prescription requesting it from a licensed physician: for those who have no physician, the county health officer or his clinic physician makes the examination.

DR. IRVING W. POTTER, BUFFALO, N. Y.—In Buffalo, an investigator, partly paid by the County Society has the duty to report the maternal deaths. The committee members study these reports but are not supposed to know what hospital or doctor is involved. We have to contend with many abortions. Deaths from abortion and from ectopic pregnancy are all included as maternal deaths. While this method of reporting is followed the maternal death rate is going to be high. The question of consultation in hospital cases is being considered and at the present time about half the hospitals insist upon consultations.

DR. FREDERICK H. FALLS, CHICAGO, ILL.—I speak in order to enlist your support in the various state medical societies in which you find yourselves, in interesting the members of the society to take this program of maternal welfare seriously. The Illinois State Medical Society had no committee on maternal welfare until this program was started.

It is important also for the universities of the various states to promote this program and to provide postgraduate courses. The refresher courses are not the ideal and nothing but a regular course in an educational institution will really fill the gap. Provision has to be made for the education of the physicians of the state, at very little or no cost to themselves, because the very men who need this work the most are the ones who do not have the funds or do not feel they are able to leave their practice in order to take the course.

DR. R. L. DENORMANDIE, BOSTON, MASS.—In Massachusetts we have been making a five-year study of all maternal deaths and all cesarean operations. We ask if there has been a consultation held before operation, and the answer is usually, yes. But the physician has had a consultation with his best friend. A consults with B, B consults with A. They agree. That is no true consultation such as we think should be held. Furthermore if a consultation is held with a surgeon, he will, of course, do a cesarean for that is the only obstetric operation he knows.

DR. GEORGE F. PENDLETON, KANSAS CITY, MO.—It is interesting that every speaker has dug out the facts in his own community and spoken of the theories applicable to that particular community. Now you and I cannot go home and as doctors in entirely different communities make use of the same plans that are being used in New Jersey or Illinois or some other place. We will have to investigate our own communities and find out where the special trouble is.

DR. R. T. LA VAKE, MINNEAPOLIS, MINN.—Abortion and ectopic are correctly included in computing puerperal morbidity and mortality, in the interests of maternal welfare. One of the most important aims in prenatal care is to bring it about that every woman report to a physician as soon as she suspects pregnancy, that he may impress upon her the danger of induced abortion if she is considering it, that he may give her instructions that will decrease the chance of abortion, and that he may have a chance to diagnose ectopic pregnancy early.

It is my belief that we should get more outstanding results from prenatal care teaching if we would stress, both to the patients and to the physicians, the importance of avoiding contamination of the vagina in the last three months of pregnancy, and establish in the minds of physicians and laity alike a conviction of the greater safety of nonintervention at delivery, except where clearly justifiable indications exist.

DR. J. BAY JACOBS, WASHINGTON, D. C.—Washington has had a very high infant and a relatively high maternal death rate for many years. The average

## NEW YORK OBSTETRICAL SOCIETY

*MEETING OF OCTOBER 10, 1939*

The following papers and discussions were presented:

**Chemotherapy in Obstetrics and Gynecology.** Dr. R. Gordon Douglas. (For original article, see page 275.)

**The Pharmacology of Sulfanilamide and Sulfapyridine.** Dr. E. K. Marshall, Jr. (By Invitation.)

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## OBSTETRICAL SOCIETY OF BOSTON

*MEETING OF NOVEMBER 21, 1939*

The following papers were presented:

**Report on the Cesarean Sections Done in Massachusetts in 1938.** Dr. Robert L. DeNormandie.

**The Estrin Treatment of Dysmenorrhea.** Dr. Somers Sturgis.

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## Correspondence

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*To the Editor:*

I wish to call attention to an error in a footnote of Busby and Fisher's case report, "Tubal Pregnancy Associated with Tuberculous Salpingitis," which appeared in the January, 1940, issue, page 125. In the footnote a recent report of a similar case is attributed to Dr. Arthur Stein; the case report referred to, however, was published by me in the December, 1939, issue, page 1068, and was submitted for publication in May, 1939.

I noted from these reports that my patient was admitted to Michael Reese Hospital, Chicago, on February 16, 1939, Busby and Fisher's patient was admitted to Victoria Hospital on February 17, 1939, and furthermore, Stevenson and Wharton's article on the subject, containing their case report, appeared in the February, 1939, issue of THE AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY. This is indeed an interesting coincidence in point of time.

IRVING F. STEIN, M.D.

*Chicago, January 23, 1940.*

# Society Transactions

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## AMERICAN ASSOCIATION OF OBSTETRICIANS, GYNECOLOGISTS AND ABDOMINAL SURGEONS

### FIFTY-SECOND ANNUAL MEETING

HOT SPRINGS, VA., SEPTEMBER 7, 8 and 9, 1939

The following papers were presented:

**Blood Lipids in Pregnancy.** Drs. Otto H. Schwarz, S. D. Soule, Bernice Dunie, St. Louis, Mo. (For original article, see page 203.)

**Treatment of Hemorrhagic Disease of the Newborn.** Dr. W. R. Barney.

**Vulvovaginal Mycoses in Pregnancy.** Drs. B. Carter, C. P. Jones, R. A. Ross, and W. L. Thomas, Durham, N. C. (For original article, see page 213.)

**Tracheloplasty (Sturmdorf Technique) in the Treatment of Sterility.** Dr. Oren Moore, Charlotte, N. C. (By invitation.) (For original article, see page 269.)

**Stereoroentgenography of 400 Pelves With Clinical Correlation.** Dr. John G. Walsh, Providence, R. I. (By invitation.) (For original article, see page 255.)

**Hermaphroditism.** Drs. Herbert Schmitz and J. P. Greenhill.

**Inversion of the Uterus.** Dr. Louis E. Phaneuf. (Published in *Surgery, Gynecology and Obstetrics*.)

**A Study of Uterine Defense Mechanism.** Dr. James R. Goodall.

**President's Address.** Dr. James E. King, Buffalo, N. Y. (For original article, see page 179.)

**Rationale for the Use of Testosterone Propionate in the Immediate Treatment of Excessive Uterine Bleeding.** Dr. A. R. Abarbanel, New York, N. Y. (For original article, see page 243.)

**Struma Ovarii.** Drs. H. M. N. Wynne, James S. McCartney and J. H. McClen-don, Minneapolis, Minn. (For original article, see page 263.)

**The Interrelationship of Surgical Conditions of the Pelvic and Abdominal Viscera.** Dr. W. S. Bainbridge. (Published in *J. Internat. Col. Surg.* 2: 417.)

**Is There a Clinical Relationship Between Pyelitis of Pregnancy and Pre-eclamptic Toxemia?** Drs. R. D. Mussey and S. B. Lovelady, Rochester, Minn. (For original article, see page 236.)

**Studies of the Urinary Tract After Delivery.** Drs. W. T. McConnell and L. A. Gray, Louisville, Ky. (For original article, see page 227.)

**Spontaneous Rupture of the Uterus.** Dr. Joseph W. O'Connor.

**The Physiology of the Anterior Pituitary and a Note on the Medullotrophic Hormone.** Dr. J. B. Collip, Montreal, Canada. (For original article, see page 187.)

**Maternal Welfare Work, What Are Its Fruits?** Dr. James K. Quigley, Rochester, N. Y. (For original article, see page 349.)

**An Electric Timer as An Aid in Counting the Fetal Heart in the Second Stage of Labor and in Spacing and Timing Forceps Traction.** Dr. Walter B. Mount, Montclair, N. J. (For original article, see page 272.)



This is in striking contrast to the statement usually made that a mole is found only once in 2,000 or 3,000 pregnancies. The authors are convinced that a molar change is responsible for many abortions in the early months of pregnancy. Since the diagnosis of molar change may be made with the naked eye only in a few cases, histologic study is necessary to prove this point in most cases. Hence, all tissue obtained at miscarriages should be examined microscopically as a routine. This procedure is particularly important in view of the possibility that a chorion epithelioma may follow a hydatid mole.

J. P. GREENHILL.

**Young, James:** *The Habitual Abortion and Stillbirth Syndrome and Late Pregnancy Toxaemia*, Brit. M. J. 1: 953, 1937.

Much evidence has accumulated within recent years consistent with the view that an important cause of the habitual abortion-stillbirth syndrome, which has baffled the obstetrician in the past, is a disturbance in the metabolism of pregnancy, in which a deficiency of vitamin E is involved. This evidence challenges the role which vitamin E plays in the prolactin-progesterone mechanism of pregnancy.

The author cites cases showing favorable results in clinical application.

Some evidence is further offered for the view that similar circumstances may supply the missing X factor which was previously described for the nontoxic recurrence of abortion, stillbirth, and accidental hemorrhage in women who are subject to eclampsia and pre-eclampsia. This evidence provides the view that major degrees of deficiency tend towards interruption of pregnancy in the early months without toxic manifestations, whereas if the deficiency is less marked, the pregnancy is capable of progressing to the later months with a consequent risk of toxemia.

These views raise a question as to the part played by diet in fertility, and more especially as to how far changes in the consumption of essential dietetic elements may have contributed to the declining birth rate.

F. L. ADAIR AND S. A. PEARL.

**Currie, David:** *Vitamin E in the Treatment of Habitual Abortion*, Brit. M. J. 2: 1218, 1937.

The author reviews the broadening concepts of general vitamin therapy. He points out work done, showing that vitamin E bears more resemblance to the luteal hormone (progesterin) than to other hormones as regards clinical features, physiologic properties and clinical significance.

Over 50 women were given wheat germ oil during pregnancy, but he includes in his summary only 37 who had aborted more than once. Habitual abortion implies that more than one pregnancy has failed to go to term. Of these 37, who had collectively 130 pregnancies, only 16 viable children resulted. Under treatment these women produced 37 living children. Two of these women aborted; there were 2 sets of twins; and 4 children died in the hospital from prematurity. The appearance of albuminuria of a severe degree was a new problem that arose during treatment. Five patients showed gross signs of toxemia.

He concludes that vitamin E appears to be a definite step forward in the treatment of this most distressing condition of habitual abortion. He advises a dose of 3 minims of the oil extract daily throughout the entire pregnancy, but adds that the dosage and length of time of administering are open to discussion.

F. L. ADAIR AND J. A. HAUGEN.

**Kunz, A. C.:** *Functional Insufficiency of Anterior Pituitary as Cause of Habitual Abortion*, Zentralbl. f. Gynäk. 61: 2004, 1937.

In 30 cases of habitual abortion Kunz employed bed rest, corpus luteum extract, and then daily intramuscular injections of prolactin until the end of the fourth month of pregnancy. All of the abortions in these women had occurred

# Department of Reviews and Abstracts

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CONDUCTED BY HUGO EHRENFEST, M.D.

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## Selected Abstracts

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### Abortion

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Report by British Abortion Committee, Editorial, Brit. M. J. 1: 1183, 1939.

This article is an editorial comment on the report of the Committee on Abortion, asked by the Home Secretary and Minister of Health to inquire into the prevalence of abortion, the laws relating thereto and recommendations for better enforcement of the laws.

The Committee strongly recommends amendment of the present law so that a medical practitioner who induces abortion to safeguard or restore his patient's health does not render himself liable to prosecution. The Committee implies in its report that it favors legalization of abortion for the relief of conditions that carry a threat to health as well as those that directly threaten life. Because of the possibility of the abuse of such legislation, the Committee recommends control by making consultation prior to abortion obligatory as well as notification of the medical officer of health or other qualified persons. The Committee is not unanimous in its recommendation that such reports of abortion be made available to the police.

The Committee could only make a rough estimate of the frequency of abortion, believing it to be 110,000 to 150,000 per annum, and because of its limitations in arriving at a satisfactory figure, it cannot determine the mortality rate. However, from the evidence available, the Committee concludes that criminal abortion has not become more frequent in recent years but that it is attended by a high degree of risk not only to health but to life.

FRED L. ADAIR AND JOHN NEWDORP.

Grace, W. H.: *The Pathological Aspects of Criminal Abortion*, Liverpool Med. Chir. J. 45: 136, 1937.

This is a discussion of the legal aspects of abortion from the standpoint of the pathologist. Two types of death are described: (1) a quick death due to shock or, rarely, air embolism and (2) a lingering death due to sepsis. The methods of producing abortion are classified as (1) external violence, (2) administration of drugs, and (3) mechanical injuries to the uterus and its contents by (a) direct violence and (b) injection of fluids. The importance of considering these possible methods at the time of post-mortem examination is emphasized.

CARL P. HUBER.

Keller, R., and Adrian, J.: *Molar Degeneration in the Etiology of Early Abortion*, Gynec. et obst. 38: 332, 1938.

Histologic examination of early ovular remains revealed Keller and Adrian the great frequency of molar degeneration. They decided to determine whether such molar changes might not be the cause of many unexplained abortions in the early months of pregnancy. Among 305 curettements for incomplete abortions they found fresh villi in only 96 cases. Among the latter cases there were 21 patients with molar degeneration. In 5 patients all the villi had undergone degeneration whereas in 16 cases only part of the villi manifested degenerative changes. Hence 21 specimens among 305 (6.8 per cent) showed molar alterations.

admitted to a hospital in an industrial town some 40 per cent are probably procured. The history in such cases is usually freely given, but it is unreliable. The commonest cause in the locality in question is the insertion of slippery elm bark into the cervical canal.

Local interference is usually performed with some mechanical skill, and it is rare to find positive evidence of injury. This indicates that it is more frequently done by someone other than the woman herself. Local sepsis is exceedingly common. Uterine sepsis and pyrexia were present in 35 per cent of the cases, and uterine sepsis without a temperature in a further 10 per cent.

Of the series, 20 per cent of the patients were decidedly ill and 3 per cent died. All the deaths were due to sepsis, except one which resulted from chronic nephritis and uremia. Interesting is one case in which the patient introduced thin slippery elm through the urethra into the bladder. She went to term but was later operated upon for stone of the bladder.

F. L. ADAIR AND S. A. PEARL.

Holtz, F.: *The Treatment of Abortion*, Acta obst. et gynec. Scandinav. 18: 245, 1938.

The author followed up a series of 2,718 abortion cases, some as long as four years. He came to the conclusion that in cases of early abortion without complications and without severe bleeding the interference should be prompt. He is of this opinion because after active therapy there is less frequent spread of infection, a lower mortality, a shorter stay in the hospital and a lower incidence of sterility. When intervention was practiced after a prolonged course, the results were less favorable because there were more infections, more cases of secondary anemia, a longer stay in bed and a higher frequency of sterility.

In late abortions, however, expectant treatment gave better results than active therapy. In most cases both the fetus and the placenta were expelled spontaneously. In cases where the placenta was retained, active treatment was much more satisfactory than conservative therapy.

J. P. GREENHILL.

Hüsey, P.: *Abortion and Accidents*, Monatschr. f. Geburtsh. u. Gynäk. 108: 1, 1938.

In the opinion of Hüsey an abortion rarely is the result of an accident. Even where an abortion follows an accident, the psychic fear plays a greater rôle than the trauma to the body. The world literature offers abundant evidence that even the severest forms of trauma may not interfere with pregnancy because the ovum is very well protected. Gestations are terminated following injuries, chiefly in women who have a tendency to abort. It is very important to rule out all illnesses which may possibly bring about interruption of pregnancy. In order for an abortion to be attributed to an accident it must take place within twenty-four hours of the accident and the physician must rule out any serious illness and predisposition on the part of the patient to abort. Furthermore, criminal attempts to empty the uterus must also be eliminated. Fever is nearly always an indication of mechanical interference.

J. P. GREENHILL.

Petersen, E.: *The Use of Spinal Anesthesia for Induced Abortion*, Acta. obst. et gynec. Scandinav. 17: 449, 1937.

Spinal anesthesia was used by Petersen in 22 cases where an abortion was induced. In all the patients the bleeding was much less than it is when the operation is performed under general anesthesia.

J. P. GREENHILL.

during the second to the fourth month of pregnancy but all were able to carry their pregnancies to full term for the first time under this form of treatment.

It is well known that the corpus luteum hormone favors and protects nidation of an ovum and that estrogenic hormone does the reverse. However, after the second month of pregnancy the corpus luteum is not essential in women. Thus, Ask-Upmark reported 51 cases in which the corpus luteum was extirpated after the second month of pregnancy, and abortion resulted in only one case.

Kunz believes that habitual abortion is due to functional insufficiency of the anterior lobe. In support of this idea is the fact that most abortions occur in the first half of pregnancy, the period during which the greatest demands are made on the pituitary gland. For this reason the author gives prolan during the first four months of pregnancy to all women who have had abortions.

J. P. GREENHILL.

Rosenfeld, S. S.: Habitual Abortion. Treatment by Injection of Pregnancy Serum, *New York State J. Med.* 38: 440, 1938.

The author has been treating 20 cases of habitual abortion with about 5 c.c. of normal pregnancy serum injected intramuscularly once a week. Should staining or bleeding occur during the course of pregnancy, the patient is put to bed and doses up to 10 c.c. may be given two or three times a week or even daily, depending on the signs and symptoms. In the absence of bleeding, patients are permitted to pursue their normal routine and duties. The diet is that usually prescribed for a normal pregnant woman, with the addition of cod liver oil and viosterol. Of the 20 patients, 19 gave birth to normal living infants.

J. P. GREENHILL.

Jones, O. Vaughan: The Oestrin Content of Blood and Urine: Its Estimation and Clinical Application, *Liverpool Med.-Chir.* 45: 112, 1937.

The presence of estrogenic hormone in the blood and urine during the menstrual cycle and during pregnancy is reviewed. An attempt to make quantitative studies of the urine by absorption spectroscopy is described. The results were promising, though in excess of values obtained by biologic and chemical methods. Actual figures are not given.

The value of blood estrin levels in cases where intrauterine death of the fetus has occurred is reported. In 12 cases of suspected missed abortion the blood was negative for estrin and macerated fetuses were subsequently delivered. In 29 cases of suspected fetal death, the blood estrin was negative in 23 with subsequent delivery of macerated fetuses, and in 6 cases the blood estrin was positive with the fetuses later found to be alive. The estrin level in the urine was not altered and the Aschheim-Zondek was not a reliable index.

CARL P. HUBER.

Mondt, W.: The Results of Expectant Treatment of Abortions, *Monatschr. f. Geburtsh. u. Gynäk.* 106: 291, 1937.

The author reports a series of 365 cases of abortion treated conservatively. He recommends that practitioners employ extremely conservative therapy of abortions. This may entail many visits and immediate activity should hemorrhage occur. Furthermore, the physician will have to be firm in his conviction in spite of the requests of the patient or her family for active treatment. The best place in which to treat abortions is a hospital. The disadvantage of the prolonged period of time necessary to treat abortions conservatively is overcome by the improved subsequent health of the patients.

J. P. GREENHILL.

Cooke, R. G.: An Analysis of 350 Cases of Abortion, *Brit. M. J.* 1: 1045, 1938.

The author analyzes 350 cases of abortion treated during eight years, 1930 to 1937, and assesses the probable cause of each. It appears that of abortions

## Books Received

ATLAS OF SURGICAL OPERATIONS. By Elliott C. Cutler, Moseley Professor of Surgery, Harvard University, etc., and Robert Zollinger, Assistant Professor of Surgery, Harvard University, etc. Numerous illustrations on 48 plates (by Mildred B. Coddington), 179 pages. Macmillan Company, New York, 1939.

OBSTETRICAL PRACTICE. By Alfred C. Beck, Professor of Obstetrics and Gynecology, Long Island College of Medicine, Brooklyn, etc. Second edition, 858 pages, 1043 illustrations. Williams and Wilkins Company, Baltimore, 1939.

PICTORIAL MIDWIFERY. By Sir Comyns Berkeley, Chairman of the Central Midwives Board, Consulting Obstetric and Gynaecological Surgeon to the Middlesex Hospital, etc. Third edition, 166 pages. Williams and Wilkins Company, Baltimore, 1939.

PRACTICAL MEDICAL DICTIONARY. By Thomas Lathrop Stedman, M.D., and Stanley Thomas Garber, M.D. Fourteenth, revised edition with etymologic and orthographic rules. Illustrated, 1303 pages. Williams and Wilkins Company, Baltimore, 1939.

OFFICE GYNECOLOGY. By J. P. Greenhill, M.D., F.A.C.S., Professor of Obstetrics and Gynecology, Loyola University Medical School, etc., Chicago, Ill. With 106 illustrations, 406 pages. The Year Book Publishers, Inc., Chicago, Ill., 1939.

THE ART OF ANAESTHESIA. By Paluel J. Flagg, M.D., Visiting Anaesthetist to Manhattan Eye and Ear Hospital, etc., New York. Sixth edition, revised, with 161 illustrations, 491 pages. J. B. Lippincott Co., Philadelphia, 1939.

OBSTETRICAL NORMAL. Professor Raul Briquet, lente catedrático de Clinica Obstétrica e Puericultura Neonatal da Universidade de S. Paulo. With 427 illustrations with 37 in colors. Livraria Editora Freitas Bastos; Rio de Janeiro, 1939.

ANNALES INSTITUTI OBSTETRICII ET GYNECOLOGICI UNIVERSITATIS, Helsingfors. Edited S. E. Wichmann. Helsinki, Univ. Frauenklinik. Tom. XI. 1935.

CAESAREAN SECTION, Lower Segment Operation. By C. McIntosh Marshall, Honorary Assistant Surgeon, Liverpool Maternity Hospital, etc. With 2 plates and 107 illustrations, 230 pages. Williams and Wilkins Company, Baltimore, 1939.

OBSTETRICAL MANIKIN PRACTICE. By Lyle G. McNeile, Professor of Obstetrics and Gynecology, University of Southern California School of Medicine, etc. With 38 illustrations, 111 pages. Williams and Wilkins Company, Baltimore, 1939.

ENDOGENE ENDOKRINOTHERAPIE IN DER GYNAEKOLOGIE. Von Jules Samuels, Chirurg-Frauenarzt, Amsterdam. A. W. Sijthoff's Uitgever-smaatschappij, Leiden, Holland, 1938.

DER ZYKLUS DER FRAU. Reform des Ehelebens. Von Dr. Jules Samuels, Amsterdam. G. Naef, The Hague, 1938.

PRIMER CONGRESO CHILENO Y AMERICANO DE CIRURGIA. Imprenta Universitaria. Santiago de Chile, 1939.

TEXTBOOK OF GYNAECOLOGY. By James Young, Professor of Obstetrics and Gynaecology, University of London, etc. Fifth edition, with 226 illustrations, 425 pages. Adam & Charles Black, Soho Square, London, 1939.

MANUAL OF PUBLIC HEALTH NURSING. Prepared by the National Organization for Public Health Nursing. Third edition, 529 pages. The Macmillan Company, New York, 1939.

JEWISH CONTRIBUTIONS TO MEDICINE IN AMERICA, from Colonial Times to the Present. By Solomon R. Kagan, M.D. Foreword by Professor James J. Walsh. Second edition, revised and enlarged. Illustrated, 792 pages. Boston Medical Publishing Company, Boston, Mass., 1939.

GYNECOLOGIC OPERATIONS and Their Topographic-Anatomic Fundamentals. By Professor Dr. Heinrich Martius, Director of Women's Clinic in Goettingen. Authorized English Translation by W. A. Newman Dorland, M.D. With 404 mostly colored illustrations, 486 pages. S. B. Debour, Publishers, Chicago, 1939.

# Items

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## American Board of Obstetrics and Gynecology

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting in Atlantic City, N. J. on June 8, 9, 10, and 11, 1940, immediately prior to the annual meeting of the American Medical Association in New York City.

Application for admission to Group A, Part II, examinations must be on file in the Secretary's Office not later than March 15, 1940. Formal notice of the time and place of these examinations will be sent each candidate several weeks in advance of the examination dates. Group A, Part II, candidates will be examined on June 8 and 9, and Group B, Part II, on June 10 and 11, 1940.

The annual dinner of the Board will be held in New York City on Wednesday evening, June 12, 1940, at the Hotel McAlpin.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh, (6) Pa.

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## Microfilm Sets of Periodicals

The Committee on Scientific Aids to Learning, President Conant of Harvard, chairman, has made a grant to cover the cost of making a microfilm master negative, on the most expensive film, of sets of volumes of scientific and learned journals.

This permits the non-profit Bibliform Service to supply microfilm copies at the sole positive copy cost, namely 1 cent per page for odd volumes, or a special rate of ½ cent per page for any properly copyable 10 or more consecutive volumes.

The number of pages will be estimated on request to: American Documentation Institute, Science Service, 2101 Constitution Ave., Washington, D. C.

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## Mississippi Valley Medical Society 1940 Essay Contest

The Mississippi Valley Medical Society offers annually a cash prize of \$100, a gold medal, and a certificate of award for the best unpublished essay on any subject of general medical interest (including medical economics) and of practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best. Contestants must be members of the American Medical Association who are residents of the United States. The winner will be invited to present his contribution before the next annual meeting of the Mississippi Valley Medical Society at Rock Island, Ill., Sept. 25 to 27, 1940. Contributions shall not exceed 5,000 words, be typewritten in English in manuscript form, submitted in five copies, and must be received not later than May 1, 1940. Further details may be secured from Dr. Harold Swanberg, Secretary, 209-224 W. C. U. Building, Quincy, Ill.

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## Erratum

In the Roster of American Obstetrical and Gynecological Societies, published in the January issue of the JOURNAL, the name of Dr. Ralph A. Reis, of Chicago, was given in error as the President of the Central Association of Obstetricians and Gynecologists. Dr. Reis occupied the office during the previous year. Dr. Jennings C. Litzenberg, of Minneapolis, is the present incumbent.

tality, and mortality in other specific diseases. While no apology is meant or implied for the extent to which women are unnecessarily sacrificed in childbirth all over our country today, it is right that we should recognize that the efforts which our profession particularly, and that of other allied agencies, have put forth to improve conditions, have not been fruitless, and do not warrant a further hopeless outlook.

So, conceding the fact that, in spite of some rather sketchy improvement, mortality rates are still too high, there is practical unanimity in the opinion that both maternal and fetal mortality is in direct proportion to the incidence of operative interference. The actual ratio of incidence of operative interference appears to vary widely.

Barrett<sup>1</sup> quotes from the Woman's Hospital in New York City a total operative incidence of 20 per cent with a gross maternal mortality of 0.46 per cent. He does not appear to include "prophylactic low forceps" in this rather high incidence. Contrasting the mortality in the spontaneous and low forceps groups together, with the mortality in the operative group, the latter is about seven times the former. He says: "Poor results in obstetrics are caused most often by the abuse rather than by the proper use of obstetric surgery." Lynch<sup>7</sup> says that "while there has been a marked increase in the trend toward radicalism in obstetrics, led by some of our trained obstetricians, there is no evidence that the trend toward radicalism has reduced maternal mortality." Fraser and Sparling<sup>3</sup> say the Canadian Government statistics show a mortality rate of 0.23 per cent in spontaneous deliveries as compared to 0.82 per cent in operative or nonspontaneous deliveries. They also point out the increasing trend toward radicalism. Plass<sup>11</sup> quotes the statistics of the State Registrar of Iowa showing almost a 12 per cent operative incidence in all deliveries in that state, with the incidence in the larger cities nearly twice that in the smaller communities. It rises to 23.1 per cent in urban hospitals, which is again nearly twice the rate in rural hospitals. John O. Polak said, "That meddlesome midwifery, with its trauma, infection, and operative risk, adds its quota to the fatalities is beyond question. . . . By increasing the operative incidence in obstetrics, maternal mortalities have been materially raised. . . . The higher the incidence of operative intervention, whether done by the expert or by the novice, the greater the increases of both the maternal and the fetal mortality." Holmes, Mussey and Adair<sup>4</sup> declare that there is an increasing tendency to resort to surgical procedures to assist and complete the delivery of the child and that this surgical intervention, often not indicated, is necessarily associated with a higher mortality among mothers. Jeff Miller<sup>9</sup> stated that other things being equal, the mechanism of a normal labor is still very much better from any angle than any of the improvements we have found for it, and called Nature the best obstetrician of us all, even in cases of definite pelvic contraction. The maternal and fetal results are far better when they deliver spontaneously than the best of surgical skill has been able to achieve. LaVake<sup>5</sup> says an increasing spirit of radicalism has clearly placed the errors and abuses of operative obstetrics in the forefront of those causes that have retarded the reduction of general maternal mortality. He quotes Schauta to the effect that spontaneous birth is by far the best solution of the many complicated problems of contracted pelvis, and that spontaneous birth is in this group of cases much more frequently possible than appears from our statistics.

The New York Academy of Medicine Committee on Public Health Relations,<sup>8</sup> in its report published in 1933, says that perhaps the most prominent feature of the development of modern obstetric practice is in the steady increase in the proportion of operative deliveries and that this tendency is regarded by most observers as one having dangerous potentialities for both mother and child. They found an average operative incidence in 75 per cent of all hospital deliveries in the metropolitan area of 24.3 per cent, and believe that the ratio of deaths following operative deliveries is about five times as great as those following spontaneous deliveries. About half the total maternal deaths followed operative deliveries. The committee reported that in their opinion 76.8 per cent of all the deaths following abnormal delivery

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## Original Communications

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### REDUCTION OF UNWARRANTED OPERATIVE INCIDENCE IN OBSTETRICS\*

S. A. COSGROVE, M.D., F.A.C.S., JERSEY CITY, N. J.

(From the Margaret Hague Maternity Hospital)

FOR many years emphasis has been placed on the allegedly unnecessarily high maternal mortality in this country. Invidious and condemnatory comparison has been made between this mortality and that of other countries. The conclusion has been repeatedly stated, on the bases of results in many individual clinics, and of various municipal and sectional surveys, that much of it depends on unnecessary and ill-judged operative interference embraced in the American management of obstetrics.

This conclusion, with its direct implication of criticism of the American practitioner, has evidently been accepted very widely by those who aspire to speak for American obstetrics, to judge by the almost numberless articles which have appeared for many years past in our literature. Apparently there was no question that the operative incidence should be reduced.

In regard to the damaging mortality rates alluded to, statistics gathered years ago, some of them by lay organizations with partisan objectives, whose methods of statistical study have been probably justly criticized, are repeatedly published. Yet Runnels<sup>13</sup> in a recent very sane study of this problem, states that the statistics of a decade ago are no longer valid, if they ever were. He shows by unbiased public records that the rate of diminution of maternal mortality in the last ten years has been in excess of the rate of diminution of general mor-

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\*Read at the First Meeting of the American Congress on Obstetrics and Gynecology, Cleveland, Ohio, September 11 to 15, 1939.

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NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."



higher, and by a fetal and infant mortality of 15 to 30 per cent. It is by no means the simple and safe procedure it is popularly supposed to be. The mortality of the average operator, and the average mortality of all operators, are much truer indices of the value of a given procedure than are the brilliant results of a single skillful surgeon or single well-organized clinic. Cesarean section by this criterion is clearly a dangerous measure. Obstetrics is still a specialty in itself, not an adjunct of general surgery. The lives of parturient women and of their children are not safe in the hands of men who so regard it."

Fraser and Sparling<sup>3</sup> state that the principles which should always govern the indications for operation are being lost sight of in the desire to deliver women through the abdomen when and if any abnormality arises. Certain published statistics show, even yet, cesarean section mortalities in certain groups of cases as high as 27 per cent. Schumann<sup>14</sup> reports the average maternal mortality throughout the United States following cesarean section at 5.8 per cent and believes that the indications for the operation have been broadened unwarrantedly. He makes the important point, however, that it is not fair to charge cesarean section with all deaths that follow this operation, irrespective of the primary cause for which the operation may have been employed. For instance, if an eclamptic patient dies after spontaneous vaginal delivery, the death is charged against eclampsia the true cause of death, and not against the method of delivery. If the same woman however, has had a cesarean section, death would be unhesitatingly charged against the type of delivery. He quotes a case in which a uterus was ruptured in an attempted forceps delivery. Cesarean hysterectomy was resorted to in a desperate attempt to save the patient's life. The attempt failed. Death was charged against the cesarean section rather than against the clumsy attempt at forceps delivery which was actually responsible. He says that much more valid information, both as to the value and the abuse of the operation, might be obtained if all statistics were broken down and respective ratios given for the purely elective group of cesarean sections and the necessitous group.

I quite concur with Schumann in this recommendation, and feel sure that such break-down could not fail to be of greatest educational value in teaching the importance of anticipating elective cesarean section by handling cases during any tentative trial of labor with proper reference to this possibility, and the avoidance of section when proper conditions for its performance do not obtain. When performed under suitable conditions, and either by predetermined election, or within a safe period of election, the broadening of the primitive indications for cesarean section is not necessarily so pernicious as some commentators have implied.

Thus Newell<sup>10</sup> admits more than a score of justifiable indications for the operation; Barrett<sup>1</sup> says that their tendency at the Woman's Hospital has been to widen its indications, and that this has not increased either their general mortality rate or their cesarean section mortality; he actually believes that it represents a conservative, rather than a radical, trend; Schumann<sup>14</sup> says: "It is my opinion, often expressed, that in women with manifest though not necessarily insuperable disproportion, whether this be of maternal or fetal origin, elective cesarean section under local anesthesia, and preferably without a preliminary test of labor, offers the best prognosis for the life and well being of the infant as well as the subsequent health of the mother"; Lull, citing a 10 per cent incidence of section in a series of personal cases, justifies it on the ground that many were referred because of predetermined abnormalities, and says, "In retrospect of these . . . cases, . . . there were none that I was sorry that I had performed cesarean section upon"; finally, I personally strongly suspect that the gentlemen who are so insistent that perhaps our patients would be better off if we returned to the indications for section of fifty years ago, would most terribly hate to be restricted to those indications in their individual practices.

could have been prevented, and that the physician was responsible in 86.8 per cent of all these preventable deaths. They say, "Clearly, a reduction of the mortality rate could be achieved by a reduction in operative interference. . . . If all women who could do so were allowed to deliver themselves spontaneously, and the indications for instrumentation were reduced to those having real validity, . . . there is every reason to believe that there would be a reduction in the deaths."

On the other hand, Lull,<sup>6</sup> while stating that he is in favor of teaching undergraduate students the most conservative type of obstetrics, believes that if a man is at all competent and is delivering all of his patients in a well-equipped modern hospital, it is justifiable to accept a high incidence of operative interference to relieve the woman as much as possible from pains of labor. He acknowledges a total forceps incidence of 45 per cent in full-term deliveries and more than one-third of this forceps interference was for the sole indication of relieving the patient of second stage labor pains. Practically all of this group would have delivered themselves if allowed to continue in labor a few more hours. He says there was no damaging trauma to either mother or child, and claims a gross maternal mortality in the whole group of a thousand cases of only 0.3 per cent.

Several years ago I heard Dr. Norris Vaux quote a moderately high operative incidence for his own clinic and say, I believe not entirely jestingly, that he not only had no apology for his rate of operative incidence but might personally prefer that it had been 100 per cent.

In connection with this whole matter of the relation of operative incidence to gross maternal mortality, one must be very careful not to draw unwarranted conclusions from the statistics. To say that operative mortalities are from 5 to 8 times those of spontaneous deliveries does not justify the superficial inference that if operative deliveries could be entirely eliminated, and all cases be permitted to deliver spontaneously, the general mortality would be reduced to that at present observed in spontaneous deliveries. Higher rates of mortality must necessarily attend the abnormalities which necessitate operative interference. The rates, therefore, which pertain to operative deliveries are susceptible of reduction only to the extent that *misapplied* operative interference can be reduced. The rate for even wholly justifiable and competently performed operative interference will of necessity always be several times higher than the rate for normal, spontaneous delivery.

In relation to the concededly too high operative incidence, most of the published comment places greatest emphasis on the abuse of cesarean section. There is almost unanimous agreement that this operation is too frequently performed; that it is performed for inadequate indications; under improper conditions; in the face of definite contradictions; by many individuals not qualified either to judge of its necessity or to properly perform it.

Newell<sup>10</sup> speaks of the prevalent abuse of one of the most valuable obstetric procedures and says that at the present time cesarean section is so misused that obstetric mortality and morbidity are increased rather than diminished, thus negating appreciation of its true value.

In the sonorous language of Jeff Miller<sup>9</sup> "It is one of the paradoxes and one of the tragedies of medicine that certain measures designed primarily as life saving and health giving, should carry in their abuse, death and invalidism; cesarean section is in this group. Originated for the salvation first of the child and then of the mother, all too frequently it has become a death-dealing agent for them both." He says it is attended by a mortality for the mother ranging from 2 to 25 per cent and

case can be decided upon its individual merits by the honest objective judgment of competent men properly trained in the fundamentals of good obstetrics.

Furthermore, no case should ever be decided with one eye on the statistics of the hospital or clinic. I have heard of a clinic wherein forceps incidence was very likely to drop if the maximum total monthly incidence considered allowable for such interference was being approached. This is indeed putting the cart before the horse. Statistics should never be computed in advance. That clinic will render the best service to humanity in which every decision as to interference is based on the best attempt possible to apply honestly good practice standards. If I could be sure that this was true of every case of such interference in my own clinic I should be perfectly happy no matter what the subsequently computed statistics showed.

How may the objectives thus outlined best be attained? All commentators are agreed that the only feasible means for achieving them are embraced in regulation and education. These are both slow processes. Because of this fact they are wholly ineffective unless persisted in with dogged determination, constant effort, repetitious reiteration and infinite patience.

A considerable start in both directions has already been made. Under the heading of regulation, the American College of Surgeons, The American Medical Association, The American Board of Obstetrics and Gynecology and The American Hospital Association have all inaugurated and are carrying forward a more or less well-integrated program. Theirs is the only source of regulatory power, except of course the possibility of direct governmental control. Through the system of approval of the hospitals by the College, the approval for residency and intern training by the Association, the direct and indirect power of these organizations is considerable. But in the very nature of things it is probably too cursory and general to be effective where it is perhaps most needed, that is to say, in the small general hospitals. Even were their scrutiny sufficiently detailed to secure the institution of ideal regulations, the effect thereof must necessarily depend upon the intelligence and spirit with which the regulations themselves are applied.

Regulatory effort, therefore, must be prepared for by a continuous intensive program of education. This program must be manifold. It is necessary to teach:

I. The laity. The program of lay education is well understood, and must impress, among other things: (1) Appreciation of the necessity of prenatal care, including instruction as to the importance of significant symptoms, such as bleeding, and those which evidence developing toxemia. (2) The fact that pregnancy and labor, while ordinarily physiologic, may at any stage become rapidly and dangerously pathologic. (3) That ordinary doctors of conscience and good training are suitable attendants, so long as reproduction remains, in all its phases, physiologic, but that in the presence of abnormalities, the experience, training and judgment of qualified obstetricians is just

But while the major furore of discussion thus rages about cesarean section, the improper use of this procedure does not by any means constitute the whole abuse of obstetric operative interference. Polak<sup>12</sup> said some years ago, "As we see it, much of the present day mortality is directly the result of the teachings of some prominent obstetricians who have been busy inventing operative procedures to control the onset of labor, or shorten or eliminate the second stage of labor, or improve the physiological mechanism of placental delivery." He then proceeded to cite induction of labor in all cases at estimated term; the promiscuous use of episiotomy; "elective" version; "prophylactic" forceps; routine manual extraction of the placenta.

The fact that different men will variously estimate the validity of any of these procedures, and the extent of their legitimate application, is beside the point. The important fact is that each of them, like cesarean section, is capable of tremendous abuse, and they are likely, of course, to be abused more widely even than section, because many a man who would not dare essay section would fail to recognize his inability to undertake procedures calling for much greater skill and carrying no less serious and certain risk. The consulting obstetrician encounters most frequently of all situations, perhaps, that in which an attendant, lacking obstetric judgment, impatiently proposes or attempts operations either not properly indicated, or before suitable conditions for their exhibition are fulfilled.

I do not believe that there can be any agreement, even among first rate minds, as to just how high operative incidence should be. Those entitled to be considered leaders in obstetric thought are agreed that a general trend toward conservatism is highly desirable; that nature is capable of delivering babies spontaneously in a surprisingly high proportion of cases; that much operative interference of all kinds, generally practiced, is unnecessary; is employed without sound consideration of proper indications and conditions; and that much of this pernicious interference with nature is based on unworthy motives such as greed, the desire for spectacular notoriety, the selfish conservation of the physician's time and energy. So far as these latter factors affect the issue, such operative interference is wholly bad.

But entire elimination of operative interference, of course, would result in a great and unnecessary increase in maternal and fetal mortality, and in impairment to the health and social usefulness of both mothers and children.

That degree of interference is therefore ideal which will least interfere with the potentially normal processes of nature; which will not per se add artificially to the hazards of mother and child; but which will, on the other hand, tend to reduce to the minimum the hazards, not only immediate, but to future health, of mother and offspring, which perverted or complicated natural processes might without interference entail.

Individual estimation of just what ratio of operative interference will best attain this ideal will present validly wide differences, in relation to the type of thought processes, the experience, and the degree of intelligence and training of different operators. Certain it is that the ideal above defined will be most closely attained when every

eral agency is capable of properly evaluating and correlating all its phases, and because only the government is able to control funds adequate for its proper fulfillment.

II. The great medical organizations already listed as regulatory agencies, allied groups in the professional field, and many lay groups, which by their altruistic interest have constituted themselves pioneers in this very important field.

All of these have already accomplished so much as to warrant a high degree of satisfaction in, and commendation for, their efforts. But such effort must be persistent and intensified all along the line, in order to achieve the utmost ultimate results.

III. The Obstetrician. The program is closest to the understanding and heart of the obstetrician himself. He must inspire all effort put forth by all of the organizations already mentioned. He must pour into the channels described all his own understanding and his own heartfelt passion for improvement.

But, in arrogating to himself the inspiration and direction of the effort toward betterment of the outlook for parturient American women and their offspring, through education, he must himself be honest in his purpose and approach. He may not say to the general practitioner, "so far must thou go" and then proceed to go himself far beyond the limits which he impresses on others.

He may not preach conservatism to his students and his fellow physicians, but exemplify in his own private practice the most extreme radicalism. He must discipline himself, in the same degree and in the same fashion that he proposes to discipline others, or his own motives and attainment will be discredited and his leadership repudiated.

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as vital to happy outcome, as are the qualifications of the neurosurgeon, the cardiologist, and the ophthalmologist, in their respective fields. (4) That, therefore, the consultative services of obstetricians are just as natural and imperative in obstetric emergencies, as are those of other specialists in the crises of medical and surgical experience. (5) The recompense of the obstetric attendant, both general practitioner and specialist, should be adequate to the attainments, time, and labor which these men employ in the proper management of situations involving the immediate life and death of two-patients-in-one, and the future welfare of both.

II. The profession must be educated. It has been recognized for a long time that undergraduate instruction in obstetrics is deficient in relation to that devoted to other branches. Much progress has been made in this direction, however, within the last two decades, and it is probable that the best of our undergraduate schools today are doing all that they can be expected to do, as to the type of undergraduate instruction, and as to the time allotment devoted to obstetrics in relation to the rest of the curriculum.

The great need in education in obstetrics in this country today is increased opportunity in internship training for the recent graduate, and in similar training for those graduates of longer experience who have not earlier received it. The present facilities for such instruction are all too meager, not only for the manifest demand of physicians of all sorts for it, but for the even more manifest need for it reflected in the statistics of obstetric results which we have already reviewed. This double need may best be met by the cooperation of the management and staff of every hospital, general or otherwise, handling any considerable amount of obstetric material. The means by which such instruction may be undertaken by these hospitals has been discussed in greater detail in an earlier paper.

A by no means negligible, but not so important phase, is the conduct of lecture courses, integrated meeting programs, seminars for practitioners under university and medical society auspices, statewide or local bases. In this connection may be mentioned the helpfulness of hospital conferences open to the profession.

III. Hospital managements must be educated to an appreciation that their contribution to social welfare is not fully met by provision of even a high type of medical, surgical, and obstetric service to their respective communities, but that just so far as they fail to develop all of the educational potentialities which their material represents, they so far fail in their service to society. It is here that the influence of the regulatory agencies will be most significant.

Those who must be responsible for this whole broad program of education are:

I. Government. The Federal Government, both directly, and by collaboration with the State Departments of Health, has already undertaken this responsibility on a broad scale. Its contribution is necessary because of the extent of the program, because only a Fed-

The Fallopian tubes are moderately frequent sites of endometriosis. This site of involvement constituted 3.2 per cent of the pronounced lesions and endometriomas of tubal stumps, usually following salpingectomy or tubal ligation, accounted for 1.1 per cent of them. Other areas of implantation were the external surface of the uterus, the broad ligament, the umbilicus, the cervix, and a laparotomy scar. Umbilical endometriosis is associated with the same condition in other locations as a rule. Three of the four cases in these series were accompanied by cul-de-sac involvement. One case of bladder endometriosis is herein recorded, which was associated with extensive cul-de-sac infiltration. Vesical transplants invade the muscular coats, but do not perforate the mucosal lining of the bladder. The cystoscopic appearance is that of one or more small elevations which vary in color from pale blue to deep purple, depending upon the phase of menstrual activity. They are situated above the inter-ureteric ridge and usually are surrounded by an area of edema but no ulceration is present.

The appendix was the seat of extensive infiltration in one patient. Any portion of the intestinal tract which lies in or near the pelvic cavity may be affected. The most frequent seat is the sigmoid or the rectum. Extensive involvement of the lower bowel may occur, with widespread adhesions, resulting in partial or complete obstruction either from acute adherent angulation or actual impingement upon the lumen of the bowel. The mucous membrane is never infiltrated and rectal bleeding usually is absent to differentiate rectal and sigmoidal endometriosis from malignancy.

#### ASSOCIATED LESIONS

A characteristic feature of endometriosis is its common association with other pelvic pathology which overshadows both the symptoms and physical findings of the adenomas. Of the 307 patients in this series only 59 (19 per cent) presented endometriosis alone while the remaining 248 patients showed a total of 367 complicating conditions, an average of 1.5 per patient (Table II). Uterine myomas predominated

TABLE II. ASSOCIATED LESIONS. (307 PATIENTS)

	PER CENT
Patients with no allied conditions	59—19
Patients with allied conditions	248—81
Number of complicating lesions	367

#### *Distribution*

	PER CENT
Myomas	63.9
Pelvic inflammation	18.7
Uterine retrodisplacement	6.9
Adenomyomas	6.5
Cervical stenosis	0.9
Ovarian cyst	3.3
Ovarian carcinoma	0.6
Umbilical endometriosis	0.9
Tuberculous endometritis	0.6
Bladder involvement	0.3
Fundal carcinoma	0.3
Ectopic pregnancy	0.3

the associated lesions. Sixty-four per cent of the 307 patients with endometriosis had fibroids. Varying forms of adnexal inflammation, usually consisting of peri-

# THE CLINICAL ASPECTS OF PELVIC ENDOMETRIOSIS\*

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THE term endometriosis is applied to a condition peculiar to women, which consists of aberrant adenomatous lesions, possessing histologic and physiologic properties similar to those of the endometrium. Usually the lesions occur in the pelvic cavity to involve one or several of the genital organs or the contiguous pelvic viscera, although the appearance of endometriosis has been reported in the gall bladder, the lungs, and even in the arm.

The well-known proclivity of endometriosis for widespread dissemination is suggestive of malignancy, but its slow growth, limited invasive properties, and dependence upon ovarian stimulation render it a benign process. Despite the limitations of benignity, no other nonmalignant growth is so capable of such widespread involvement as endometriosis. In a study of 307 patients with this condition, a total of 343 major lesions were found, and innumerable minor lesions were present that are not considered in this analysis. The ovaries were the most frequent sites of endometriosis (Table I). Unilateral ovarian involvement con-

TABLE I. LOCATION OF MAJOR LESIONS. (TOTAL NUMBER, 343)

Ovary:	PER CENT
Unilateral	36.0
Bilateral	28.0
Cul-de-sac	25.0
Fallopian tubes	3.2
Tubal stumps	1.1
External surface of uterus	2.0
Broad ligament	1.4
Rectovaginal septum	1.1
Umbilicus	1.1
Miscellaneous (cervix, 1; appendix, 1; bladder, 1; laparotomy scar, 1)	1.1

stituted 36 per cent of the lesions, and 28 per cent of the growths were bilateral. With 64 per cent of the major lesions of endometriosis located in one or both ovaries, it is obvious that ovarian tissue forms the most fertile soil for endometrial transplants.

Widespread infiltration of the cul-de-sac formed 25 per cent of the massive lesions in this study. Often this was associated with endometriosis in other situations, particularly the ovaries. At times the process extended into the rectovaginal septum, with the production of a nodular infiltration similar to that of rectal malignancy. Rectal digital and proctoscopic examinations clarify the diagnosis, for endometriosis does not infiltrate the rectal mucous membrane as does malignancy.

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Disturbance in the function of the contiguous organs, chiefly the bladder and rectum, occurred in 17.4 per cent of the patients. The rectal symptoms consisted of pressure, pain, dyschesia, increasing constipation and menstrual diarrhea. Rectal bleeding usually was absent, nor was hematuria a symptom of bladder involvement. The most frequent urinary symptoms were urgency, urinary frequency, and dysuria. Both the rectal and bladder symptoms were definitely increased at catamenia.

TABLE IV. CHIEF COMPLAINTS. (307 PATIENTS)

Total chief complaints	596
	PER CENT
Abnormal menstrual periods	56.0
Intermenstrual discomfort and pain	40.0
Dysmenorrhea	35.0
Backache	21.0
Dysfunction of contiguous organs	17.4
Pelvic tumor	12.5
Marital and fertility difficulties	6.6
Miscellaneous	7.5

Marital and fertility difficulties were present in 6.6 per cent of the cases. These consisted of dyspareunia, infertility, and repeated abortions. Although only 12 patients listed infertility as a chief complaint, it will be shown subsequently that 40 per cent of the married patients had never been pregnant.

The knowledge of a pelvic tumor was listed by 12.5 per cent of the patients as a chief complaint. The majority of these patients had uterine myomas to mask the presence of the accompanying endometriosis.

The miscellaneous complaints consisted of leucorrhea, which was coincidental, and of a menstruating sinus which occurred in four patients, three with umbilical lesions and one with endometriosis of a laparotomy scar.

### MENSTRUAL ALTERATIONS

Since alteration in the menstrual periods heads the list of complaints, the identification of a characteristic type of this anomaly would be of diagnostic value. The patients were divided into two groups, those having endometriosis plus other conditions, consisting of 248 patients, and those with uncomplicated endometriosis, numbering 59 patients (Table V). In the former group, 40 per cent had normal periods in contrast to 64 per cent of the latter group who had no menstrual abnormality. This suggests that the menstrual alterations which accompany endometriosis often

TABLE V. MENSTRUAL ALTERATIONS. (307 PATIENTS)

	ENDOMETRIOSIS PLUS ALLIED CONDITIONS 248 PATIENTS PER CENT	ENDOMETRIOSIS ALONE— 59 PATIENTS PER CENT
No alteration	40	64
Abnormal periods	60	46
Abnormalities		
Menorrhagia	61	57
Metrorrhagia	15	14
Menometrorrhagia	16	24
Oligomenorrhea	4.7	5
Amenorrhea	3.3	0

are due to the allied conditions which so frequently accompany it and not to the endometriosis per se. Comparison of the types of menstrual abnormality in the two groups shows little difference, for the various alterations occurred with equal frequency in either class. These figures indicate both the absence of a characteristic

salpingitis or perioophoritis, occurred in 19 per cent of the patients. Endosalpingitis with tubal occlusion was rare and the fimbriated extremities of the tubes generally were open.

Uterine retrodisplacement, because of its obstructive possibilities, is considered to be an active etiologic factor in pelvic endometriosis. Its occurrence in 7 per cent of the patients in this series is suggestive, since it was most common in the younger patients who presented no other likely anatomic cause for the endometriosis.

Uterine adenomyomas, which appeared in 6.5 per cent of the patients, are considered to be manifestations of endometriosis by some authors. They are not so treated in this study, as we believe that they are adenomatous growths which result from endometrial diverticula, and are not true lesions of endometriosis.

The low incidence of cervical stenosis in this series (0.9 per cent) probably does not indicate its true occurrence, for attempts to demonstrate this condition rarely were made in the care of our patients. The occurrence of 12 (4 per cent) ovarian neoplasms, 2 of which were malignant, probably is a coincidence. The possibility of malignant degeneration in ovarian endometriomas has been emphasized. While we might expect endometrial transplants to become malignant with the same frequency that the uterine endometrium does, clinical experience does not justify this expectation. Pelvic endometriosis was associated with umbilical involvement in three instances. No satisfactory explanation of this occurrence has been offered.

#### AGE DISTRIBUTION

Fundamentally endometriosis is a disease of the menstrual life. The youngest patient in this series was 18 and the oldest 62 years of age. The incidence rapidly increased from 19 per cent in the third decade to 41 per cent in the fourth, with a drop to 37 per cent in the fifth (Table III). More than three-fourths of the patients were between 30 and 50 years old. Two of the cases in the older groups

TABLE III. AGE INCIDENCE. (307 PATIENTS)

	PER CENT
Less than 20 years	0.25
20-30 years	19.0
30-40 years	41.0
40-50 years	37.5
50-60 years	2.0
More than 60 years	0.25

were postmenopausal, probably appearing as hang overs from the menstrual era. The possibility of some extraovarian stimulation must be considered in the light of numerous recent demonstrations of estrogenic activity in the blood and urine after the menopause. Furthermore, it has been suggested that some endometriomas may assume semimalignant characteristics and continue to grow following the withdrawal of ovarian stimulation.

#### CHIEF COMPLAINTS

The symptoms of endometriosis fall into three general groups: local discomfort, disturbances of genital physiology, and alterations in the function of contiguous viscera. In the present study, dual complaints were the rule. From 307 patients, 596 outstanding complaints were listed, averaging 1.9 symptoms per patient (Table IV). Alteration in the character of the menstrual periods occurred in 56 per cent of the patients, and menstruation was accompanied by extreme pain in 35 per cent of the cases. Intermenstrual discomfort or pain had an incidence of 40 per cent. The descriptions which were applied to this symptom ranged from those of simple lower abdominal discomfort, soreness, or bearing down sensations to attacks of acute pain. These symptoms usually were intensified by the menstrual periods. This also was true of the backache, which occurred in 21 per cent of the patients. The lumbar or sacral areas were the seats of the discomfort which generally was described as a boring pain that became crippling with each menstrual period.

riages at large is recognized to approximate 12 per cent, it is reasonable to deduce that the patient with endometriosis is three times more likely to be sterile than the average individual.

### PREOPERATIVE DIAGNOSIS

With the train of physical changes and functional alterations which accompany endometriosis, its diagnosis would appear to be a simple matter. This is not the case, however, for in a study of 286 patients with endometriosis, the condition was not diagnosed preoperatively in almost two-thirds of the cases (Table VIII). Among the reasons for this failure are the lack of a characteristic symptomatology and of more importance the frequent occurrence of other pelvic lesions which overshadow

TABLE VIII. PREOPERATIVE DIAGNOSIS. (NUMBER OF PATIENTS, 286)

	PER CENT	
Correctly diagnosed	104	36
Not correctly diagnosed	182	64
<i>Obscuring conditions</i>		
Myomas		65
Myomas and pelvic inflammatory disease		4
Pelvic inflammatory disease		9
Uterine retrodisplacement		8
Ovarian cyst		6
Ectopic pregnancy		4
Miscellaneous		4

the signs of endometriosis to mask its identity. Among the pelvic conditions which obscured the presence of endometriosis in this study, uterine myomas predominated to account for 69 per cent of the patients in whom endometriosis was not suspected, 4 per cent of which were associated with pelvic inflammatory disease. Simple adnexitis was associated with 9 per cent of the undiagnosed endometriosis, and in 8 per cent of the cases, uterine displacement was not thought to be complicated by endometrial transplants. The presence of benign ovarian neoplasms led the examiner astray in 6 per cent, and in 4 per cent the existence of ectopic pregnancy clouded the pelvic picture. Among the miscellaneous conditions which accounted for 4 per cent of the faulty interpretations were functional dysmenorrhea, dysfunctional bleeding, sterility, and uterine carcinoma.

### TREATMENT

Important factors in the choice of treatment are the patient's age, the severity of the symptoms and the removability of the major lesions. With reasonable certainty as to diagnosis in the absence of intolerable symptoms if ovarian involvement or other pelvic pathology does not necessitate treatment, routine observation is feasible and safe. Under such circumstances, the patients are not hospitalized, and they do not enter this statistical analysis. Endometriosis which requires treatment in young patients demands mature surgical judgment with conservatism as the guiding principle. In this study, only 14 per cent of the patients in the third decade were subjected to radical therapy, that is complete ablation of ovarian function, and 36 per cent of those in the fourth decade were treated in this manner (Table IX). The incidence of radical therapy in the older groups increased to 70 per cent where ovarian conservation is less important.

In all age groups, isolated lesions which are readily removable should be treated by extirpation. The presence of widely disseminated invasive growths, which render removal impractical or impossible, necessitates one of two alternatives: surgical intervention or irradiation. Two hundred and eighty-nine of the patients in this series were treated surgically and 15 by irradiation. Complete ovarian

menstrual aberration and the possibility that endometriosis alone often does not cause abnormal menstrual periods. When it does produce alterations, they are dysfunctional in type as the result of disturbed ovarian secretions.

### DYSMENORRHEA

Dysmenorrhea, particularly the acquired type, is recognized as being a common symptom of endometriosis and our study confirms this impression. In this analysis, the patients are divided into two groups: those with endometriosis plus allied conditions, 57 in number, and those with endometriosis alone, of which there were 48 (Table VI). In the "endometriosis plus" group, 28 per cent stated that the periods had always been painful with no appreciable recent change. This type of dysmenorrhea ("primary") occurred in only 20 per cent of those with uncomplicated endometriosis. The term "aggravated" is used to denote menstrual pain which began with puberty but subsequently became much more severe. Twenty-five per cent of the "plus group" and 39 per cent of those with no other lesion had such pain. "Acquired" dysmenorrhea was present in 47 per cent of the first group and in 41 per cent of the second. By adding the last two types, we found that newly developed menstrual pain occurred in three out of four patients with endometriosis, either in the form of acquired dysmenorrhea or intensification of a previously existing symptom.

In consideration of the time of the dysmenorrhea, 92 patients had described the relationship between the onset of the pain and the beginning of the period. Since there was no difference between those with endometriosis alone and those with complicating lesions, the groups were combined (Table VII). Intramenstrual pain lasting throughout the period led in frequency with an incidence of 50 per cent. One-fourth of the group had both pre- and intramenstrual dysmenorrhea, while only 18 per cent complained of premenstrual pain, to be relieved at the onset of the flow. Pain which developed during or at the termination of the period to persist for several days occurred in 6 per cent of the patients. These figures suggest that the characteristic time relationship of dysmenorrhea in association with endometriosis consists of its onset prior to the beginning and persistence throughout the duration of the period.

TABLE VI. TYPE OF DYSMENORRHEA

	ENDOMETRIOSIS PLUS ALLIED CONDITIONS	ENDOMETRIOSIS ALONE
NUMBER PATIENTS	57	48
Primary	28 per cent	20 per cent
Aggravated	25 per cent	39 per cent
Acquired	47 per cent	41 per cent

TABLE VII. TIME OF DYSMENORRHEA. (NUMBER OF PATIENTS, 92)

	PER CENT
Premenstrual	18.0
Pre- and intramenstrual	25.0
Intramenstrual	50.0
Intra- and postmenstrual	4.4
Postmenstrual	1.3
Intermenstrual	1.3

### STERILITY

In the analysis of the association of endometriosis and infertility, it was found that 40 per cent of the 238 married patients in this series had never been pregnant. The numerous other factors which reduce fertility were not considered nor was the incidence of involuntary sterility determined. Since the occurrence of barren mar-

inevitable. Of the 289 patients who received surgical treatment for endometriosis, there were two postoperative deaths, an incidence of 0.7 per cent.

The development of unhappy late postoperative reactions follows the lack of ovarian conservation. Our belief in the absolute value of ovarian and whenever possible, menstrual and procreative preservation is too deeply engrained to be modified. Relief of symptoms and regression of the lesions from pelvic endometriosis is assured by total ovarian ablation through the agency of surgery or irradiation. While such therapy is justifiable in the later years of life, in younger women it is to be avoided if possible. Of the 140 patients, in this study, who were treated by radical surgery or irradiation, 49 (28 per cent) complained of severe menopausal symptoms, despite the fact that such procedures were carried out for younger women in a very small percentage of cases. With the modern methods of replacement therapy, many of these patients can be restored to comfort, so far as the flushes are concerned, but the loss of menstrual and procreative functions, of course, is irreparable.

Furthermore, the results of conservatism in the treatment of endometriosis justify its continuation. The 149 conservatively treated patients with adequate follow-up data are divided into three groups: Those with conservation of both uterine and ovarian function, those with preservation only of ovarian function, and a small group with extensive cul-de-sac involvement which is considered separately.

In the first two classes, Group A, with conservation of menstrual function consists of 49 patients, and Group B, with ovarian preservation alone, of 76 patients (Table XI). In Group A, relief of symptoms reached 67 per cent and partial relief 26 per cent, while in Group B complete relief was noted by 93 per cent and

TABLE XI. RESULTS OF TREATMENT, CONSERVATIVE, SURGICAL

	UTERUS AND ONE OR BOTH OVARIES CONSERVED GROUP A	ONE OVARY CONSERVED GROUP B
Number of patients with adequate follow-up	48	76
Relief of chief complaints	67%	93%
Partial relief	26%	5%
No relief	7%	2%
Residual Pain	15%	7%
Dysmenorrhea	23%	0%
Regular periods	79%	14%
Irregular periods	21%	2%
No periods	0%	84%
Pregnancies	10 (21%)	0%
Growth of lesions	7 (15%)	2 (2.6%)
Treatment		
Irradiation	2	0
Surgery	5	2

partial relief by 5 per cent. The incidence of residual pain was twice as great in Group A as in Group B, 15 per cent against 7 per cent. Almost one-fourth of the Group A patients had postoperative dysmenorrhea. In Group A, 15 per cent of the patients required subsequent treatment usually because of increased residual lesions which produced symptoms, while only 3 per cent of the Group B needed further treatment. Thus far, the comparison indicates the desirability of the less conservative procedure, but the next item, subsequent pregnancies, of which there were 10 (21 per cent) in Group A, and, of course, none in Group B, liberally compensates for the higher percentage of postoperative complaints and subsequent treatments in the first group. For young women with endometriosis, surgical conservatism should give way to radicalism only when practice of the former is found to be utterly unfeasible at the operating table.

The therapeutic results in endometriosis of the cul-de-sac and rectovaginal septum are sufficiently interesting to justify separate consideration. Many of the patients in this group presented endometriosis elsewhere, as well as extensive lesions

TABLE IX. TREATMENT ACCORDING TO AGE. (304 PATIENTS)

AGE	~20	20-30	30-40	40-50	50-60	60-70
Number of patients	1	56	124	115	7	1
Radical	0%	14%	36%	70%	72%	100%
Conservative	100%	86%	64%	30%	28%	0%

TABLE X. TREATMENT ACCORDING TO THE MAJOR INVOLVEMENT

	NUMBER OF PATIENTS	TREATMENT			
		SURGERY		IRRADIATION	
		RADICAL PER CENT	CONSERVATIVE PER CENT	RADICAL PER CENT	CONSERVATIVE PER CENT
Ovarian	243	51	49	0	0
Cul-de-sac and Rectovaginal septum	47	13	62	15	10
Miscellaneous	14	0	80	14	6

ablation was necessary in 48 per cent of the surgical subjects and in 60 per cent of those who received x-ray or radium therapy.

Since ovarian endometriomas are removable, the preferred treatment for this condition is surgical (Table X). Two hundred and forty-three patients with ovarian endometriosis were operated upon. Bilateral oophorectomy was necessary in 51 per cent, and in 49 per cent, it was possible to conserve one ovary and often the uterus. In young women, for whom conservation of menstrual and procreative functions is so important, unilateral oophorectomy with resection or cautery destruction of transplants, or small endometrial cysts, in the other ovary frequently can be performed. This has been done many times, even in the presence of cul-de-sac transplants, and its importance and feasibility in the surgical treatment of endometriosis cannot be too strongly emphasized.

Endometriosis of the cul-de-sac or rectovaginal septum may be treated by irradiation or by surgery. In the older patients, surgical, or irradiative castration is inevitably curative. For younger patients, with no doubt as to diagnosis, active treatment is indicated only in the presence of definite symptoms. Of the 47 patients in this series who required therapy, three-fourths were treated by surgery and one-fourth by irradiation. The majority of the patients with massive cul-de-sac infiltration who were operated upon received the benefit of conservative procedures. Of those treated by irradiation, the preponderance was given castration doses. The group which received submenopausal doses consisted largely of young women with cul-de-sac transplants who complained of menorrhagia or dysmenorrhea, for whom small doses of intrauterine radium were applied.

The miscellaneous group consists of umbilical, incisional, cervical, vesical, and postsalpingectomy endometriosis. The majority of these patients were young, for whom local excision with ovarian conservation was desirable and practical. Those treated by irradiative castration presented cervical or vesical involvement which necessitated the destruction of ovarian function to insure regression of the lesion.

#### RESULTS OF TREATMENT

Evaluation of the therapeutic results in endometriosis involves consideration of the following factors: the morbidity and mortality, the unpleasant late postoperative effects, the relief of symptoms, the preservation of genital functions, and the necessity for subsequent therapy. The operative treatment frequently is attended by considerable technical difficulty because of dense adhesions between the lesions and the contiguous pelvic structures. The postoperative morbidity exceeds that following more clean-cut pelvic surgical procedures and an occasional mortality is

It is a disease of middle and late menstrual life, with an incidence of approximately 80 per cent between the fourth and sixth decades.

Additional pelvic pathology accompanies endometriosis in four-fifths of the cases to obscure its presence and to cloud the diagnostic picture.

The chief symptoms of endometriosis are those of local pain, alterations in the menstrual and reproductive processes, and dysfunction of the contiguous organs.

The treatment, which may be that of routine observation, surgical intervention, or irradiation, depends upon the severity of the symptoms, the patient's age, and the removability of the major lesions.

Conservatism, particularly in young patients, with preservation of ovarian and, if possible, menstrual and procreative functions is justified by the results: 90 per cent to 95 per cent complete or partial relief of symptoms, 8 per cent necessity for further treatment, and 9 per cent subsequent pregnancies.

133 SOUTH 36th STREET

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## FETAL MORTALITY\*

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THE incidence of stillbirths and neonatal deaths has been reduced little, if any, despite the great attention given to this phase of obstetrics during the past twenty years. During the years 1935 to 1937, inclusive, there were 187,165 living births in the Province of Ontario, and during the same period there were 6,162 stillbirths and 5,988 babies died during the first month of life. How to reduce this great loss of life is a question yet unanswered, and it is possible that the study of fetal mortality from the larger centers may provide the material on which sound practice can be based. The present paper is an attempt to analyze the stillbirths and neonatal deaths in the public wards of the Toronto General Hospital for the four years, 1935 to 1938, inclusive. During that time, there were 3,745 deliveries, of which 149 were stillbirths and 80 were neonatal deaths, giving a fetal mortality of 6.1 per cent. This mortality rate has remained at approximately that figure for the last ten years. During these ten years, there have been several changes in our obstetric practice, the principal one being a more conservative attitude regarding the indications for cesarean section, and during the last five years our incidence of cesarean section has dropped from 4.9 to 1.9 per cent of our deliveries. Our attitude regarding heart disease and pregnancy and the treatment of placenta previa has accounted for the biggest part of this drop. In spite of this change in policy, our fetal mortality has remained the same.

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in the cul-de-sac. Since local excision of the cul-de-sac transplants is impractical, the only means of ablation consists of termination of ovarian function by either irradiation or surgical extirpation. Such a procedure often is not necessary, for the pelvic symptoms frequently arise from the associated pelvic condition and they are relieved by its correction. Consequently, 72 per cent of the patients in this group were treated conservatively and in only 28 per cent was radical therapy necessary (Table XII). Adequate follow-up was obtained upon 43 of the 47 patients. Conservative surgical treatment upon 25 patients resulted in complete symptom relief in 72 per cent and partial relief in 20 per cent. Subsequent pregnancies occurred in 12 per cent to justify the conservative treatment. Study of the behavior of the cul-de-sac lesions showed a decrease in only 19 per cent with no change, or an increase, in 81 per cent. Despite the lack of involution, subsequent treatment was necessary in only 12 per cent to verify the belief that cul-de-sac endometriosis frequently does not produce crippling symptoms.

TABLE XII. ENDOMETRIOSIS OF CUL-DE-SAC AND RECTOVAGINAL SEPTUM.

## RESULTS OF TREATMENT (47 PATIENTS)

Radical	13 (28%)
Conservative	34 (72%)

	SURGICAL		IRRADIATION	
	CONSERVATIVE	RADICAL	CONSERVATIVE	RADICAL
Number of patients with adequate follow-up	25	6	5	7
Relief of chief complaints	72%	100%	60%	86%
Partial relief	20%	0%	20%	14%
No relief	8%	0%	20%	0%
Behavior of Lesion				
Decrease	19%	100%	60%	86%
No change	76%	0%	0%	14%
Increase	5%	0%	40%	0%
Unknown				0%
Pregnancies	12%	0%	0%	0%
Subsequent treatment	12%	0%	0%	14%
Irradiation	1	0%	0%	1
Surgery	2	0%	0%	0%

In the irradiation group, which is too small for statistical analysis, 5 were given submenopausal doses and 80 per cent of these were completely or partially relieved of symptoms. Of the 7 patients who received menopausal values, 6 were relieved completely. One, with extensive endometriosis of the rectovaginal septum, did not respond to intrauterine radium, and subsequent destructive doses of roentgen therapy resulted in regression with relief of symptoms.

By considering the patients according to conservative therapeutic procedures, either surgical or irradiative, the results are seen at a glance. In the surgical group, 81 per cent were completely relieved of symptoms, as were 80 per cent of those treated by irradiation. Subsequent treatment was necessary in 8 per cent of the surgical group, but justification is found in 13 (9 per cent) subsequent pregnancies and in freedom from severe menopausal reactions. No subsequent therapy was required in the irradiation group.

## SUMMARY AND CONCLUSIONS

Pelvic endometriosis is characterized by the potential multiplicity of its sites of invasion. The majority of the lesions occur in the ovaries and the cul-de-sac, but any of the pelvic structures or the contiguous viscera may be affected.



It is possible that the economic conditions under which public ward patients live may play some part in causing premature labor, for it is our impression that such labors occur more frequently in public than in private practice. A dietary study of public ward patients on relief is being made at the present time, and there is some evidence already accumulated that when undernourished patients are supplied with an adequate diet, the fetus as well as the mother, is benefited, and premature labor is less frequent.

#### FETAL DEFORMITIES

The second commonest cause of death was deformities incompatible with life, of which there were 37. In some of these, there were additional factors, such as breech, forceps, version, and craniotomy, but obviously the deformity was the essential factor. The study of developmental abnormalities is of considerable academic interest, but its prevention remains a closed book, except where hereditary influence might suggest the advisability of avoiding pregnancy. In this series of 37 deformities, there were 4 cases of accidental hemorrhage, 1 of placenta previa, 9 with hydramnios, 4 of late toxemia, 1 mother had epilepsy, and 1 was in a case of twins, the second child being normal.

#### TOXEMIA OF PREGNANCY

The late toxemia of pregnancy accounted for 21 deaths. There were 198 cases of toxemia treated in the wards during that time with 45 premature births, of whom 17 died. There were actually 37 stillbirths in this group of 198 cases, but death was assigned to other causes in 16 cases. We do not know how to prevent the toxemia of pregnancy, and pre-eclamptic toxemia plays a large part in fetal mortality. It causes many intrauterine deaths and results in a considerable number of premature births. When this condition develops, the first responsibility of the obstetrician is the life and future well-being of the mother, and the welfare of the child is of secondary importance. In such conditions it is unfair to attribute the fetal death to such things as induction of labor, a breech delivery, a long labor, or cesarean section. The early toxemias cause little danger to the fetus except in those few cases where therapeutic abortion becomes necessary. In the four years under review, there were 132 cases of vomiting of pregnancy treated in the wards, and in 9 of these the pregnancy was terminated.

#### SYPHILIS

The influence of syphilis as a determining factor in fetal and neonatal deaths has almost disappeared in this clinic. Only 1 death in this series was due to syphilis and that was in a patient who had been under intensive treatment for some considerable time before pregnancy, but in whom a negative Wassermann could not be obtained. It was a breech delivery, but syphilis accounted for the fetal death. In 2,904 Wassermann tests on obstetric patients, there were only 29 positive results, and for ten years only about 1 per cent of our obstetric patients have had positive Wassermann reactions.

#### BREECH DELIVERY

Breech deliveries resulted in 32 of our deaths, and Table III is an analysis of these cases.

It will be noted that in these 32 breech cases, breech extraction is listed as having been performed 12 times. By breech extraction is meant those cases in which some operative manipulation was carried out; in the other 20 cases there was no manipulation except for episiotomy and pressure on the fundus. Only the last 7 of these deaths could be attributed to the breech delivery. The 3 cases of cerebral hemorrhage all followed breech extraction, the babies weighing 9 pounds, 9 pounds, and 4 pounds 10 ounces, respectively. Only 1 of the three was a primipara, and it was the only case of cerebral hemorrhage in which the diagnosis was confirmed at autopsy.

TABLE I. FETAL MORTALITY IN 3,745 DELIVERIES, 1935 TO 1938, INCLUSIVE

Stillbirths		149
A. Before Labor	77	
B. During Labor	72	
Neonatal Deaths		80
		229 6.1%

The causes of these 229 deaths are given in Table II. It is often difficult to be accurate in assigning the essential cause of fetal death, because more than one factor is present in many cases. For instance, toxemia of pregnancy and prematurity, placenta previa and breech delivery, or fetal deformity and long labor occurred in several of our cases, but we have given what we think was the essential reason for the fetal death.

TABLE II. CAUSES OF 229 FETAL DEATHS, 1935 TO 1938, INCLUSIVE

CAUSE	VERTEX	BREECH	SECTION	OTHER PRESENTA- TIONS	TOTAL
Prematurity	38	8	2	1	49
Fetal deformities	28	5	2	2	37
Cerebral hemorrhage	19	3	1	1	24
Toxemia	17	4	—	—	21
Accidental hemorrhage	17	3	—	—	20
Macerated fetus	13	4	—	—	17
Unknown	12	—	4	1	17
Long labor	9	—	—	1	10
Placenta previa	8	—	—	1	9
Atelectasis	2	1	2	1	6
Prolapse of cord	3	1	—	—	4
Asphyxia	—	2	—	2	4
Icterus gravis	2	—	—	—	2
Craniotomy	1	—	1	—	2
Syphilis	—	1	—	—	1
Diarrhea	1	—	—	—	1
Nephritis	1	—	—	—	1
Pernicious anemia	1	—	—	—	1
Maternal pneumonia	1	—	—	—	1
Ruptured uterus	—	—	—	1	1
Pemphigus	1	—	—	—	1
	174	32	12	11	229

## PREMATURITY

It will be seen that prematurity was the commonest cause of death in this series. We have tried to make this figure as accurate as possible, by omitting from that group premature infants in cases of placenta previa, of accidental hemorrhage, and of toxemia of pregnancy where labor was prematurely induced. All public ward patients who are six months or more advanced in pregnancy are admitted to the obstetric wards, and, as a result, there are a considerable number of very small babies included in these figures. Forty of these 49 patients had antenatal care in our own clinic, so the lack of such care was not a great factor, and our results in the care of the premature infant are very satisfactory. In the four years under review, there were 212 infants admitted to the "premature room," weighing under 5 pounds, of whom 28 died. Moreover, 74 of these babies weighed less than 4 pounds, 20 of whom died and 54 went home in good condition. One of these babies weighed 1 pound 15 ounces at birth and was discharged weighing 8 pounds 4 ounces. All babies on our service pass into the care of the Pediatric Service as soon as they enter the nursery, and the credit for the results with our premature infants is due Dr. Alan Brown and his associates.

TABLE IV. FETAL DEATHS IN CESAREAN SECTION, 1935 TO 1938, INCLUSIVE

CAUSE OF DEATH		INDICATION FOR SECTION	
Unknown	4	Contracted pelvis	5
Deformities	2	Accidental hemorrhage	3
Atelectasis	2	Ruptured uterus	2
Prematurity	2	Placenta previa	1
Cerebral hemorrhage	1	Carcinomatosis	1
Ruptured uterus	1		

proportion as operations of election, 1 patient being a repeat section done before labor began. The case with cerebral hemorrhage was done early in labor, and at autopsy there were also found petechial hemorrhages in the pleura and the abdominal cavity. It was probably a case of hemorrhagic diathesis occurring before labor. If we eliminate these cases where section was done for accidental hemorrhage, placenta previa, and ruptured uterus, we still find 6 fetal deaths following cesarean section in this series, which is an indication that abdominal delivery by no means guarantees the life of the baby.

#### ABNORMAL PRESENTATIONS OTHER THAN BREECH

Table V is a summary of fetal deaths in cases of abnormal presentation, other than breech. In this group there were 7 stillbirths and 4 neonatal deaths. In Table V, the cause of death occurs opposite the type of delivery.

TABLE V. ABNORMAL PRESENTATIONS, 1935 TO 1938

PRESENTATIONS	DELIVERY	CAUSE OF DEATH	
Face	1 Spontaneous	Deformity	1
	2 Forceps	Asphyxia	1
		Atelectasis	1
	3 Version	Long Labor	1
		Placenta previa	1
		Unknown	1
Transverse	2 Version	Ruptured uterus	1
		Asphyxia	1
	1 Embryotomy	Deformity	1
Brow	2 Forceps	Cerebral hemorrhage	1
		Prematurity	1

It will be noted that in these 11 cases causes other than the presentation accounted for 5 of the fetal deaths; namely, deformity 2, placenta previa 1, ruptured uterus 1, and prematurity 1. The 3 patients with transverse presentations entered the hospital after having been in labor for some considerable time. Face, brow, and transverse presentations present difficult obstetric problems, and the operative procedure necessary will result in death of some babies. Each case is a problem in itself, and in many instances the life of the mother is the immediate concern of the obstetrician. Any analysis of fetal mortality in which fetal deaths are tabulated as due to the method of the delivery, without consideration of the indications, is fallacious. The mere fact that many stillbirths occur after operative delivery does not necessarily mean that this method of treatment was incorrect, since operative intervention is obviously more frequent in complicated cases. It is true that infant mortality is great following high forceps delivery, yet the only alternative in most of these cases is version and extraction, where the fetal death rate will be equally high.

#### FORCEPS DELIVERY

It is obvious that where forceps delivery is practiced only upon definite indications, the infant mortality will be higher than where the so-called "prophylactic" forceps operation is done. If we eliminate prophylactic forceps, all analyses of

TABLE III. FETAL MORTALITY IN BREECH DELIVERIES

STILLBIRTHS 25, NEONATAL DEATHS 7, TOTAL 32	
Spontaneous Delivery 20, Breech Extraction 12	
CAUSE OF DEATH	
Prematurity	8
Fetal deformity	5
Macerated fetus	4
Toxemia of pregnancy	4
Accidental hemorrhage	3
Syphilis	1
Cerebral hemorrhage	3
Asphyxia	2
Atelectasis	1
Prolapse of cord	1
	32

External version is attempted on breech cases whenever feasible, but it is often impossible to accomplish, and in others the condition recurs after the baby has been turned. It is our belief that cesarean section in the interest of the baby, in breech cases, is rarely indicated, although we realize that however skillful the obstetrician, the fetal mortality in breech deliveries will always be higher than in vertex presentations. An exaggerated idea of the value of the infant's life compared to increased danger to the mother has been one factor in the great increase in cesarean section. It is probably true, in general, that where the maternal death rate is high, the fetal mortality will also be high, which is indicative of the fact that conservative obstetric practice is safest for mother and child. Nevertheless, in some centers there is a relatively high maternal mortality and a relatively low fetal death rate. In such instances there is a question whether an additional risk has not been placed upon the mother in the interest of the child. We have come to realize that breech delivery with the premature child requires greater skill in many instances than with the mature baby. The diameter of the head in a premature child is greater than the hips, and the child's body may slip through the cervix before the latter is completely dilated. We have now made it a rule that a staff member must be present at breech deliveries in all cases of premature labor.

#### PROLONGED LABOR

Prolonged labor was the cause of death in 10 cases. Of these, 9 were vertex presentations and one was a brow. Six of the vertex cases were occipitoanterior positions, 1 was R.O.T., 1 was L.O.P., and 1 was R.O.P. In our experience, therefore, occipitoposterior position is not an important cause of fetal death, and a long first stage is usually due to the cervix rather than to the position of the head. Of these 229 fetal deaths, 7 occurred in persistent occipitoposterior positions, 3 of whom had spontaneous deliveries. One occiput posterior was in a patient with eclampsia, in whom labor lasted seventy-seven hours, and 1 was in a patient with accidental hemorrhage in whom labor lasted fourteen hours. It cannot be denied that prolonged labor jeopardizes the life of the baby, but attempts to shorten such labors, except by cesarean section, carry an even greater danger to the child's life as well as increasing the maternal risk. The problem of the slowly dilating cervix is yet unsolved, but the conservative obstetrician does not feel that cesarean section is the proper solution.

#### CESAREAN SECTION

There were 12 deaths following cesarean section, of which 6 were stillbirths and 6 were neonatal deaths. These are tabulated in Table IV.

It will be seen that there were 4 fetal deaths from unknown causes in patients delivered by cesarean section, and in 2 of these the section was done for dis-

3. Prematurity has been the commonest cause of fetal mortality in our experience. The incidence of premature labors may be reduced to some slight extent by prenatal care, but the care of the premature baby offers the greatest hope of reducing this cause of fetal death.

4. Complications of pregnancy and labor inevitably increase the danger to the baby as well as to the mother. In the management of such complications, the wise obstetrician is mostly concerned with a correct obstetric judgment.

5. In obstetric complications, skill in judgment is often of more importance than technical dexterity, but this is more difficult to acquire.

## ASPHYXIA OF THE FETUS AND THE NEWBORN INFANT\*

### A STUDY OF THE CLINICAL AND PATHOLOGIC CHANGES PRODUCED BY INTRAUTERINE ASPHYXIA DUE TO PLACENTA PREVIA AND A CONSIDERATION OF METHODS TO PREVENT OR MINIMIZE FETAL ANOXEMIA

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**I**NTRAUTERINE asphyxia is known to produce physiologic and pathologic changes involving every organ and tissue in the body. It is the cause of a vast number of fetal deaths and is responsible for much of the morbidity and mortality encountered in both premature and full-term infants. Fetal asphyxia is being mentioned increasingly as an important etiologic factor in many neurologic conditions encountered in older age groups.

There are many important aspects of this condition that should receive more careful study. Much can be accomplished along obstetric lines to minimize the effects of unavoidable intrauterine asphyxia in some patients and to prevent the occurrence of fetal asphyxia in others. It is suggested that when advances are made in the prevention and management of fetal asphyxia the reward will be a significant drop in fetal and neonatal mortality and morbidity.

Intranterine asphyxia is ordinarily considered with relation to its effect on isolated organs or tissues, such as the lungs or brain; or in its relation to isolated diagnoses, such as asphyxia neonatorum or atelectasis. At the present time evidence is being accumulated to show that intranterine asphyxia should be considered as affecting every organ and tissue in the body to a varying and unpredictable degree.

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fetal deaths will show that twice as many follow operative as follow normal delivery. Nevertheless, failure to do a forceps delivery when there is delay in the second stage subjects the child to even greater danger. We have the feeling that certainly one, and possibly two, of the fetal deaths in this series might have been avoided had forceps been applied somewhat earlier. Skill in the application of the forceps and in the subsequent delivery lessens the chance of injury to the baby. The frequent mistake of a young operator is the rapidity with which he delivers after having made his forceps application. There were 28 cases in which fetal death followed forceps delivery. Of these, 24 were vertex presentations, 2 were face presentations, and 2 presented as brow.

#### ANTE-PARTUM HEMORRHAGE

There were 29 fetal deaths in which the mother suffered from ante-partum hemorrhage, 20 of these being accidental hemorrhage and 9 of them placenta previa. In these cases the life of the mother is the prime consideration. In severe cases of accidental hemorrhage, the child is practically always dead and unless routine section is done, about 25 per cent of the children will not survive, and even if section is done, the fetal mortality will still be high. In occasional cases, the welfare of the baby is the determining factor in the method of treatment, but such cases are rare in this clinic where we have no routine method of treating placenta previa, but attempt to use that method which we feel is most applicable to the given case.

#### CEREBRAL HEMORRHAGE

Table VI is an analysis of all the cases of cerebral hemorrhage of which there were 23.

TABLE VI. CEREBRAL HEMORRHAGE, 1935 TO 1938

PRESENTATION		DELIVERY	
Vertex	19	Spontaneous	10
		Forceps	7
		Version	2
Breech	3	Extraction	3
Transverse	1	Version	1
	23		23

Of these 23 deaths, 13 were stillbirths and 10 were neonatal deaths. The diagnosis was confirmed by autopsy in 12 cases, and in the other 11 there was either a clinical diagnosis alone or a clinical diagnosis substantiated by a spinal puncture. It is interesting to note that of these 23 cases, 19 were vertex presentations and 10 of them followed spontaneous delivery. However, this does not mean that these were easy normal labors, although some were in that category. Others were hard labors with prolonged first stage, and although the loss of fetal life is regrettable in these cases, yet we feel that cesarean section was not indicated, and we are also of the opinion that any attempt at delivery per vaginam before the cervix was dilated would not have decreased the danger to the child. There is the occasional case of labor in a primipara with a slowly dilating cervix, where section may be indicated in the interest of the child, but in our practice such cases are few in number.

#### SUMMARY

1. In this analysis of 229 fetal and neonatal deaths during the last four years, an attempt has been made to evaluate factors responsible for the infant mortality.

2. A reduction of fetal mortality is highly desirable, but care must be taken that efforts to reduce the number of fetal deaths do not lead to radical measures endangering the mother.

fluid may be observed in the subcutaneous tissues, in the muscles of the extremities and the heart, in the periadrenal, the peripancreatic and the retroperitoneal tissue. It may be seen in the capsule or stroma of the adrenals, the thymus, the liver, and the pancreas. Edema of the pleura, the lung stroma or parenchyma and the brain may be observed. The peritoneal, the pleural, and the pericardial cavities may show considerable free fluid, while the subarachnoid space shows an increased amount of cerebrospinal fluid. The accumulation of edema fluid contributes to the increased weight observed in the various organs.

In the third stage there is the liberation of smaller or larger numbers of red blood cells either through diapedesis or actual rupture of small vessels. The hemorrhage may be of the petechial variety and be found scattered through the various organs to a greater or less degree. The hemorrhage may be more extensive and be found in the parenchyma of the lungs, the liver, and in the intestinal tract. Alveolar hemorrhage may occur, ranging from occasional areas of extravasated blood to true alveolar hemorrhage. The cerebrospinal fluid may contain a small amount of microscopic blood, slight gross blood staining, or a large amount of free blood. The brain itself may show scattered petechial hemorrhages or at times a large accumulation of blood in the ventricles.

In the fourth stage evidence of actual tissue necrosis may be found. The liver seems particularly susceptible and shows fatty infiltration of varying degree or a marked necrosis and dissolution of tissue accompanied by hemorrhage. The brain may show changes ranging from areas of ganglion cell degeneration to widespread encephalomalacia.

The clinical manifestations encountered depend on the degree and extent of the underlying pathologic changes. The central nervous system changes account for the difficulty in resuscitation, the alteration in respiratory rate and rhythm, the loss of muscle tone and the development of convulsive movements. The congestion, edema and hemorrhage, seen generally in the various organs, when occurring in the lungs render them incapable of normal expansion and result in massive atelectasis with its attending clinical manifestations. With only the anterior margins and a few central lobules of the lungs expanded, normal oxygenation of the newborn's blood is impossible; anoxemia after birth is therefore substituted for the preceding interference with fetal circulation. The extrauterine anoxemia may well be of greater severity than the initiating fetal process and be largely responsible for the progressive fatal development.

An appreciation of the widespread pathologic changes that may be produced by asphyxia is of great practical help in the diagnosis and treatment of abnormal symptoms as they appear in the newborn.

#### THE CONTROL OR PREVENTION OF FETAL ASPHYXIA

The harmful effects of intrauterine asphyxia on the fetus and newborn infant are so real that normal labor should be managed in such a way as to keep this asphyxia at a minimum or, if possible, to prevent

SUMMARY OF THE CLINICAL FINDINGS FOLLOWING INTRAUTERINE  
ASPHYXIA DUE TO PLACENTA PREVIA

The clinical and post-mortem findings associated with fetal asphyxia due to hemorrhage from placenta previa have been studied in 11 infants, all delivered by cesarean section prior to the onset of labor. It is of practical importance that in this series of fatal cases the asphyxia accompanying partial interference with placental circulation produced no significant alteration of the fetal heart and in no instance was meconium passed. This, in spite of the fact that 8 of the 11 infants required resuscitation at birth while one other, not recorded as requiring resuscitation, was cyanotic and in poor condition from birth.

Six of the 11 infants were in poor condition from birth and lived from four to thirty-six hours. They exhibited respiratory distress with labored, grunting breathing, dilatation of the alae nasi and marked retraction of the costal margins. They were subject to varying degrees of cyanosis; their cries were feeble, their reflexes were absent and their muscles hypotonic. The majority showed petechial hemorrhages and subcutaneous ecchymosis. One vomited blood while 2 developed tense and bulging anterior fontanels, later shown to be due to a marked accumulation of clear cerebrospinal fluid.

Three infants were considered to be in fair condition for several hours following their resuscitation at birth, except for labored respirations and cyanosis of the extremities. Severe respiratory embarrassment then developed, accompanied by retraction of the costal margins and recurring attacks of generalized cyanosis. One infant developed petechial hemorrhages in the skin and scleroderma; one became spastic and had convulsive twitchings while the third developed melena and bled from the nose. They died between the ages of 6 and 36 hours.

The remaining two infants breathed spontaneously at birth and were considered to be normal for several hours. They then developed the same syndrome of respiratory distress characteristic of the rest of the group. One infant bled from the nose and mouth and into the subcutaneous tissue of the thorax before his death at twelve hours. The second infant developed labored respirations at two hours of age; at seventeen hours the respiratory distress was marked and the anterior fontanel became full; at 3 days the fontanel became tense, and apnea, cyanosis, scleremia, and generalized muscular rigidity developed. Lumbar puncture produced a bloody cerebrospinal fluid containing 50 per cent crenated red blood cells per cubic millimeter. The baby died at the age of six days. Among other findings the autopsy showed hemorrhage in the subarachnoid space and into the ventricles as well as an extreme degree of encephalomalacia.

SUMMARY OF THE PATHOLOGIC FINDINGS FOLLOWING INTRAUTERINE  
ASPHYXIA DUE TO PLACENTA PREVIA

Interference with placental circulation as the result of hemorrhage from placenta previa apparently produces in the fetus an initial state of intense blood vessel congestion that may be followed by the liberation of edema fluid, hemorrhage, and even tissue necrosis. The phase of blood vessel congestion involves all organs and tissues and extends to the finest capillaries. This stasis and pooling is largely responsible for the observed increase in weight of the lungs, the liver, and the heart and for the less marked increased weight noted for the brain, the spleen, the kidney, and the thymus.

The second stage is characterized by the liberation of edema fluid into the tissue spaces, the tissues and the body cavities. This edema



of anesthesia to the delivery of the infant is usually about four minutes and this interval is so brief that no signs of fetal asphyxia are produced. When a longer period of anesthesia is required for delivery, great care must be exercised to keep the oxygen content above 15 per cent; complete relaxation is obtained by adding ether to the mixture. The lapsed time from induction of anesthesia to delivery must be kept as short as consistent with safety. That these principles are sound is attested by the fact that in the past two and one-half years there have been 24 infants weighing less than 5 pounds delivered by cesarean section in this hospital with a gross infant mortality of 16.5 per cent.

Asphyxia may produce sufficient injury to the respiratory center to delay or prevent the normal development of extrauterine breathing. Morphine and excessive ether administration likewise may inhibit the respiratory center of the fetus. In this hospital no opium derivative is administered to a mother within four hours of the anticipated birth of her child except under rare circumstances. The anesthetists strive to keep the total amount of ether administered during any delivery at an absolute minimum. The barbiturates result in sleepy babies, and although we have observed no ill effects from their use in normal full-term deliveries, we discourage their use in premature deliveries as being a possible and unnecessary hazard.

The practice of abnormally prolonging the second stage of labor by pressure on the perineum accompanied by general anesthesia, should be discouraged as it may produce a serious degree of fetal asphyxia. I am indebted to Dr. Frederic Schreiber for permission to report an illustrative case.

A baby was seen when fifteen hours old because of convulsions and constant twitching of all extremities. The color was good but the respirations were grunting. All extremities were spastic and the eyes were held to the right in spasms. The story obtained was that the child's head had been held back and nitrous oxide given for one-half hour until the arrival of the attending physician. The baby was born spontaneously as soon as perineal pressure was released and anesthesia discontinued. The appearance was that of asphyxia pallida; the baby began breathing only after fifteen minutes of resuscitation. The baby died after forty-eight hours. There was no gross intracranial hemorrhage. All the organs showed the changes associated with asphyxia as already described in this paper. Dr. Gabriel Steiner described the microscopic sections of the brain. Two devastation areas associated with asphyxia were found in the region of the X nucleus in the medulla, on the right side, probably responsible for the infant's death. There were extensive changes, secondary to asphyxia, in the frontal and motor cortex. Had this child lived, it could be expected to show spasticity, convulsions, or mental retardation, depending on the location and extent of the lesions.

Conversely, if the cervix is fully dilated, shortening of the second stage of labor by low forceps delivery and episiotomy can reasonably be expected to reduce the incidence and degree of fetal asphyxia.

Careful study of the complications of pregnancy that are each potential causes of fetal asphyxia may result in methods of obstetric management equally beneficial to mother and child. Irving's contribution to the management of placenta previa is an example of such an approach.

it altogether. Judicious choice of anesthetics and their skilled administration will prevent injurious fetal asphyxia occurring in many cases.

Nitrous oxide and oxygen is widely used, both as an anesthetic and as an analgesic agent. Every anesthetist so using it in pregnancy should be familiar with Eastman's conclusions: "Nitrous oxide mixtures, administered to mothers in proportions of 85:15 or weaker, and for periods of less than five minutes, regularly cause moderate degrees of fetal anoxemia, but the normal, full-term infant is apparently not harmed. When nitrous oxide is given in concentrations of 90:10 or stronger, over periods which exceed five minutes, marked degrees of fetal anoxemia are produced in about one baby out of three and occasionally profound asphyxia neonatorum results."

Other methods of obtaining obstetric anesthesia or analgesia must be appraised not only from the point of view of their effect on the mother, but also as to their possible effects on the fetus. At first consideration spinal anesthesia should be particularly satisfactory for the fetus, but in practice the fall in maternal blood pressure that occasionally occurs has produced most severe fetal asphyxia. Theoretically cyclopropane would seem to be ideal for the fetus because of the high oxygen content in the anesthetic mixture. In practice there is reason to believe that it also is responsible for severe fetal asphyxia (C. A. Smith), due to the fact that it produces such marked capillary dilatation that the venous and arterial blood are practically indistinguishable. The blood circulates through the capillary bed of the placenta so rapidly that the fetus fails to receive an adequate oxygen supply.

In an earlier communication, a mortality of 54 per cent was reported from this hospital for infants weighing 5 pounds or less when delivered by cesarean section. At that time it was pointed out that cesarean section theoretically should have been the safest method for the delivery of a premature infant, since it eliminated the factor of traumatic injury. It was suggested, however, that the unexpectedly high mortality might have been due to the substitution of an even greater fetal hazard, asphyxia, for that of trauma. The intrauterine asphyxia was felt to be at times the result of the method of anesthesia employed.

Since that time methods of anesthesia have been sought that would permit satisfactory maternal anesthesia without producing harmful fetal asphyxia. The most successful methods thus far encountered are local anesthesia and rapid nitrous oxide-oxygen-ether anesthesia. The local anesthesia technique is time consuming and requires great cooperation on the part of the patient. Under the rapid method of anesthesia the mother usually receives no preliminary medication and is brought to the operating room completely conscious; she is then scrubbed and draped; the operating team stands by, scrubbed and ready to begin the operation; all these preparations being completed, anesthesia is then induced. Surgical anesthesia is produced as rapidly as possible and the section performed. The time elapsed from the start

asphyxia, yet at the same time safeguard the mother's welfare. In the case of intrauterine asphyxia, resulting from placenta previa, such a study has produced a plan of treatment beneficial to both mother and child.

The prevention of intrauterine asphyxia or the minimizing of its effects when unavoidably present should result in a real reduction in fetal and neonatal morbidity and mortality.

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1101 BEACON STREET

## THE CONTROL OF CANCER IN WOMEN FROM THE MEDICAL VIEWPOINT\*

WITH SPECIAL REFERENCE TO THE SCHILLER TEST AND THE COLPOSCOPE

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CANCER is the second most frequent cause of death in this country. It has risen from tenth place to its present position in the short space of thirty years. Only heart disease now exceeds it. In women death from cancer of the female genital organs is steadily increasing, in spite of all our efforts to control it. There was a mortality of 16,442 in 1930, with yearly increase to 19,198 in 1935 or 13 per cent more than six years previously. Cancer of the uterus alone caused 15,853 or 82.5 per cent of these deaths.<sup>1</sup> There is little doubt that in many instances death might have been avoided, had these women realized the seriousness of their early symptoms and placed themselves under competent medical care before the disease had progressed to a hopeless stage.

We do not know the primary cause of cancer. We do know, however, that carcinoma will result from chronic irritation, for it has been produced experimentally in this way. Cancer developing in locations subjected to repeated injury or at the site of chronic inflammatory lesions is a quite common clinical observation. The physician's efforts in the control of cancer, therefore, must be directed, first, toward the eradication of known predisposing lesions, second, toward the detection of early cancer, third, toward prompt and efficient management as soon as a diagnosis is made, and fourth, toward cancer education of the public.

Gynecologic cancer may be avoided largely if chronic inflammatory processes and irritation be eliminated. Examples of such influences are cancer of the vulva which develops most frequently in women who have had chronic inflammatory diseases, such as leucoplakie vulvitis.<sup>2</sup>

\*Read at the First American Congress on Obstetrics and Gynecology; held at Cleveland, Ohio, September 11 to 15, 1939.

Irving studied 308 cases of placenta previa equally divided into three chronologic groups, with each group representing a different method of obstetric management. The method of treatment employed was found to exert a marked influence on both the maternal and net fetal and neonatal mortality as shown in Table I. The

TABLE I. THE INFLUENCE OF THE METHOD OF MANAGING PLACENTA PREVIA ON THE MATERNAL, FETAL, AND NEONATAL MORTALITY

	CASES	BAGGING	A. F.†	B. H. V.†	E. T.†	C. S.†	M. M.†	NET FETAL AND NEO- NATAL MORT.*
		%	%	%	%	%	%	%
1916-23	105	44.8	32.4	1.0	1.0	2.9	7.6	47.0
1924-29	103	40.8	3.9	24.3	1.1	21.4	11.6	31.1
1930-34	100	16.0	0.0	23.0	6.0	56.0	2.0	20.3

\*Infants weighing less than 4 pounds, those dead on admission, and those with gross malformations are excluded.

†A.F., accouchement forcé; B.H.V., Braxton Hicks' version; E.T., expectant treatment; C.S., cesarean section; M.M., maternal mortality.

successful plan of treatment was as follows: Patients revealing no evidence of uterine infections with infants thought to have a good chance of survival were all delivered by cesarean section; similar patients with dead infants, with infants estimated to weigh less than 4 pounds or with infants grossly malformed at x-ray examination, were all delivered by Braxton Hicks version or by using the Voorhees' bag. Infected patients were delivered by cesarean section followed by hysterectomy with drainage, whatever the fetal condition. This plan of treating placental previa not only resulted in a reduction of net fetal and neonatal mortality from 47 to 20 per cent, but also in a reduction of maternal mortality from 12 to 2 per cent.

### CONCLUSIONS

Intrauterine asphyxia produces fetal damage proportional to the degree and duration of the anoxemia and to the susceptibility of the individual fetus.

A hypothetical explanation of the physiology of asphyxial injury is presented. As the result of asphyxia every organ and tissue of the fetus is subjected to a varying degree of vascular congestion; with further continuation of the asphyxia, every organ and tissue may develop a varying degree of edema, hemorrhage, and cell injury. The resulting clinical manifestations are dependent on the degree and extent of the underlying pathologic changes.

The prevention of fetal asphyxia demands methods of obstetric anesthesia and analgesia that do not produce fetal anoxemia or injure the fetal respiratory center.

The practice of holding the head back and abnormally prolonging the second stage of labor may produce a dangerous degree of fetal asphyxia and should be abolished. Efforts should be made to shorten the second stage when conditions are favorable.

A varying amount of fetal anoxemia is an unavoidable part of certain complications of pregnancy. The ideal method of obstetric management under those conditions represents a different individual problem for each complication. In general, a method of treatment will be sought that will minimize the degree and duration of the intrauterine

are seen for the first time in an advanced stage of the disease. Seventy per cent of the 154 patients with cervical cancer seen in our clinic since 1930 showed the carcinoma to have spread definitely beyond the confines of the cervix.

Various attempts are being made to diagnose cervical carcinoma before such gross changes have occurred.

It is thought by Hinselmann, Schiller and others that beginning carcinomas have the appearance of leucoplakia before they can be recognized grossly. Hinselmann devised a colposcope which magnifies the mucosa of the cervix to aid in detecting such lesions. He reported having observed six patients with leucoplakia in 1926 who four years later developed cancer of the cervix.<sup>8</sup>

Schiller advocates the application of Grams iodine stain for the detection of such lesions. Normal cells stain a deep mahogany brown, while those of cancerous nature, due to their lack of glycogen, do not stain so well. Schiller believes that 30 per cent of all cases of beginning carcinoma give this whitish or unstained appearance. He further states that the earliest stage of cervical cancer is characterized by surface epithelium that has the cytologic characteristics of carcinoma. In 1937 he reported that he had discovered 130 cases of early carcinoma by this method. From 1928 to 1931 there were 51, of which 49 were alive and healthy, a five-year survival of 96 per cent.<sup>9</sup>

Because of considerable variation in thought of gynecologists and pathologists as to the practicability and value of these tests, the author secured a cross section of opinion of 11 teachers located in different centers of the United States and pre-eminent in the field of gynecologic cancer.

They were first questioned regarding their experience with the Schiller test, the percentage that had proved malignant, and what value they placed on this test as a means of early diagnosis. Many interesting and valuable comments were received.<sup>10</sup>

All had had experience with the test. As to the number of malignancies found, nine had either found none, very few, or were unable to say. Two made definite statements: The first, Lynch, having had 184 consecutive cases, found four early cancers without gross evidence of the disease. Three of these gave a positive Schiller test and the other did not. The second, Falls, using the routine test, states that when the test is positive, if an infected laceration is present, he removes a cone of cervix which is systematically studied. Not more than 5 per cent of these tissues showing a positive reaction proved to be cancerous.

Six men stated that the test was of value in identifying areas for biopsy, however, one of these, Miller, had given it up, after using it for some time, stating that it was of little additional help in his diagnostic work. The other 5 stated that they placed no value on it. Interesting comments were made on the biopsy findings, two stating that relatively few had proved malignant, another that the biopsies did not confirm the supposed cancer, and a fourth, that not all cervixes giving positive tests have been proved cancerous and that not all cancerous cervixes have given positive tests. Healy answered, "We have not picked up a single instance of cervical cancer with the Schiller Test."

Ninety-five per cent of cancer of the cervix occurs in women who have damaged and diseased cervices.

Graves found only two women in 6,000 who had had cervical repairs and who later developed cancer of this structure. On the other hand, in cervical cancer he found less than 2 per cent who had had cervical injuries properly repaired.<sup>3</sup> In studying the histories of 375 women with cervical cancer, Lynch found only 6 who had had injuries of the cervix corrected.<sup>4</sup> Bland reports 13,747 patients, having damaged and diseased cervices, efficiently treated, with only 11 developing carcinoma.<sup>5</sup>

The value of periodic examinations in the control of cancer is being more widely appreciated as time goes on and statistics are accumulated. An outstanding study of this type in relation to uterine carcinoma is now being conducted by Dr. Catherine MacFarlane at the Women's Medical College of Philadelphia.<sup>6</sup> One thousand white women between the ages of 30 and 80 years are having such examinations at six-month intervals for a period of five years. Significant pathology has been found in 25 per cent of these volunteers, consisting of erosions or inflammatory lesions of the cervix, polypoid growths and leucoplakia. Four instances of early cancer have been found. Commenting on this work, Dr. Ludwig Hektorn, Director of the National Advisory Cancer Council in a personal communication, asks this question, "Would not projects of this kind for the most unfavorably situated of our women, tend to meet a great need?"

The physician in his daily contact with women may do much to educate them regarding the value of periodic physical examinations.

Intelligent obstetric care is important in cancer control. The immediate repair of cervical injuries would close these gaping wounds of the cervix, which if left, become chronically infected and offer such a menace to the woman's future security. Such procedures may be done safely in hospitals, however, the risk of infection in homes seems too great to warrant repair under such conditions. This speaks for the wider use of hospitals in maternity care. Post-partum supervision offers an opportunity to correct significant pathology, such as extensive cervical lacerations, erosions, or endocervicitis. Through periodic examinations, the cervix should then be maintained in the healthiest condition possible.

The early diagnosis of gynecologic cancer is the physicians' great responsibility. Symptoms which give the slightest suspicion of malignancy demand an immediate investigation. The family physician here plays a most important role, for he is usually first consulted.

Because cancer of the uterus is the most common malignancy and its early diagnosis difficult to make, methods of early detection are important. Cervical carcinoma occurs five to six times as frequently as it does in the uterine body. Injuries and infection are undoubtedly responsible for its more frequent occurrence here.

The earliest gross appearance of cervical carcinoma is as a friable nodule, with the surface epithelium usually broken down or partially so, and any manipulation causes it to bleed. Such a malignant nodule eventually goes on to an everting or inverting type of growth, later to result in ulceration and crater formation. Unfortunately, most patients

Realizing that the control of cancer in women at the present time is inadequate and unsatisfactory, the gynecologists of this country eagerly seek the cooperation of all lay or professional groups in reducing this high mortality rate. To those who have given serious thought to this subject, there is but one conclusion. This is the great need of education regarding cancer; education of women regarding the early signs and symptoms, education of physicians in the methods of early diagnosis and proper manner of treatment, and education of hospital administrators as to the need of proper equipment to aid the physician in carrying out these measures. The American Society for the Control of Cancer has ably waged a campaign of education for more than twenty-five years. Despite their efforts toward making women symptom conscious, there are still large numbers who disregard the danger signals.

Because vaginal discharge and bleeding are the earliest manifestations of most gynecologic cancers, a campaign of education of what to expect and what not to expect during menstrual life should be waged relentlessly until it reaches all classes of individuals. The majority of women in our clinic with uterine cancer are seen for the first time in an advanced stage of the disease. In discussing this fact with such patients, there seems to be several reasons for this delay. (1) Women are accustomed to vaginal discharges, so place little importance to this occurrence unless it produces discomfort, or hemorrhage occurs. (2) It is customary for them to ascribe such symptoms to the change of life, if they be anywhere near that age. (3) They seek advice from older women who comfort them by saying they had experienced similar symptoms at this time of life. (4) They unfortunately experience no pain in the early stages, important because discomfort would cause them to seek medical advice which might save them from a cancer death. (5) Some fear the diagnosis and the possibility that an operation might be advised. (6) The cost of the physician's examination prevents others from having an investigation, for to them, they have what seems but trivial symptoms.

If we accept these observations as true and hope to correct such erroneous ideas, it is my opinion that we must give our whole-hearted support to educational movements. A comprehensive course in female physiology as it pertains to the genital organs could well be a required high school subject for all girl students. Such a course should not only include the normal physiology but emphasize the possible significance of the abnormal in its relation to malignant disease. The importance of the physicians' early investigation of abnormal discharges or bleeding from the genital organs, especially those occurring during the third, fourth, and fifth decades of life, should be particularly stressed. There is little excuse for not educating young women regarding the behavior of this fatal disease. Our inability to conquer the cancer problem, lies in the fact that women in general do not appreciate the significance of the early symptoms of carcinoma. Were such a course established, such teaching should result in a better informed, more cooperative class of women later in life. They would understand the necessity of periodic examinations and of consulting a competent physician at the first ap-

It is obvious from the experience of these men who have all put the Schiller test to trial, that they have not been able to duplicate Schiller's findings of so many early superficial carcinomas. This makes one wonder if actual cancer was present in the 51 patients in whom Schiller reported a 96 per cent, five-year survival.

The chief value of this test seems to be in indicating suspicious areas from which biopsies may be taken and to demonstrate the involved mucous membrane at the edges of early carcinoma. A few early cancers have been found by this method which would not have been recognized grossly, therefore, the test merits recognition.

Questions were asked regarding the use and value of the colposcope. Only two of the eleven consider this instrument of enough value to use routinely. The objection voiced by one (Miller), who formerly used it a great deal and gave it up, is that it is open to the same objections found in high powered stethoscopes and like instruments. It has been our experience that the colposcope is time consuming and the findings difficult of interpretation. Strong illumination has most of its advantages and none of its disadvantages.

Finally, they were questioned as to their method of dealing with leucoplakia of the cervix. There was little variation of opinion here, nearly all advised biopsy, and if the lesion proved to be benign, destruction of the area with cautery, or surgical removal. From this, it is apparent that leucoplakia is universally looked upon with suspicion because of the uncertainty of its behavior; however, most stated they had seen but few such lesions.

At present, careful study of the cervix with the naked eye, under strong illumination, with biopsy of suspicious areas and microscopic examination, is the most dependable method of early diagnosis.

The early detection of carcinoma of the uterine body must necessarily be made by diagnostic curettage. Women in whom bloody vaginal discharge occurs after the menopause have carcinoma in most instances and the diagnosis should be considered cancer until curettage proves the presence or absence of malignant tissue. It is important to remember that cancer of the fundus may develop during menstrual life, manifesting itself by intermenstrual bleeding, and a diagnosis can only be made from an endometrial biopsy obtained by curettage. Twenty-five per cent of the patients in our clinic with recorded cancer of the fundus were still in menstrual life.

A better understanding on the part of physicians as to the proper methods of treatment would do much in the control of malignancies. This applies particularly to the limitations of surgery in cancer of the cervix. There is also need for improvement in the training of medical students in the management of this disease. Attendance at cancer clinics should be required and instructions given in methods of diagnosis and treatment. Cancer clinics in which the radiologist and roentgenologist, the pathologist, and the gynecologic surgeon cooperate in studying cases and directing the treatment are the most satisfactory. Following the initial treatment, such patients should be examined periodically for recurrent lesions, and the indicated treatment immediately instituted.



## THE DETECTION OF THE RUPTURE OF FETAL MEMBRANES WITH THE NITRAZINE INDICATOR\*

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THE obstetrician is frequently confronted with the question of whether or not the bag of waters has ruptured, and much hinges on this point as to the subsequent course of treatment. In particular, this knowledge carries great weight as to the advisability of performing a cesarean section. The patient's word that she has been dripping water cannot be used as a criterion, as frequently in the later stages of pregnancy a relative incontinence develops as the fetal head settles down against the bladder. A large amount of cervical and vaginal mucus may be interpreted as leakage of amniotic fluid. Thus a test by which this information can be accurately determined would be of great value.

In recent years several such tests have been reported, all with an uniformly high percentage of accuracy. The most popular scheme relied upon the alteration in the hydrogen ion concentration of the vaginal vault, occurring subsequent to the passage of amniotic fluid from the amniotic sac. Temesvary<sup>1</sup> (1933) was among the first to perceive the value of this change and applied it to a clinical purpose. He used an indicator dye, bromthymol blue, to detect the change in pH, and out of 131 cases he reported an error of only 5 per cent. Berlind<sup>2</sup> (1932), Bock<sup>3</sup> (1934), and King<sup>4</sup> (1935) supported this high percentage of accuracy with their statistical evidences. Philipp<sup>5</sup> (1929) sought for lanugo and uric acid crystals under the microscope to determine whether or not the bag of waters had broken. Numers<sup>6</sup> (1936) based the identification of fat particles of the vernix caseosa in the vagina as a sign of the rupture of the sac.

In the Los Angeles County General Hospital Obstetrical Service the bromthymol blue test as described by King was used on a number of questionable cases of ruptured membranes. King used sterilized cotton applicators that have previously been dipped in 0.2 per cent bromthymol blue (dibromthymolsulphonphthalein) in alcoholic solution. The applicator was inserted into the vagina for one minute and the change in color from orange to blue green denoted rupture of the fetal membranes. Color unchanged signified intact membranes. He reported one false positive out of 141 patients with intact membranes, and nine false negatives from 161 patients with membranes ruptured; a percentage accuracy of 99.3 per cent and 94.7 per cent, respectively. Although no statistical studies were made of King's test at this institution, the accuracy of the test in many cases was not comparable to that of King's report. The frequent occurrence of false negatives rendered the value of the test questionable.

\*Studies made and data collected at the Los Angeles City Maternity Service and the Obstetrical Department of the Los Angeles County General Hospital, 1937 to 1938.

This is submitted to the Faculty of the Graduate School of Medicine of the University of Pennsylvania in partial fulfillment of the requirements for the degree of Master of Medical Science (M.Sc. [Med.]) for graduate work in obstetrics.

pearance of significant symptoms. The physician has but little chance to help unless the patient presents herself early in this disease. A recent statement by a New York journalist clearly sums up the situation as it exists today, "We are faced with the paradox that the most important part of the cancer fight, lies in the nonmedical field, that all of the radium, x-rays and most skillful surgery in the world are of no avail unless the public can be educated."

#### CONCLUSIONS

1. Physicians should instruct their women patients to undergo periodic examinations, at which time a careful investigation of the pelvis should not be omitted. Strict attention should be paid to the elimination of chronic inflammatory lesions.

2. The immediate repair of cervical injuries following childbirth should be done when surroundings permit. The post-partum elimination of cervical erosions, endocervicitis, and infected lacerations are important in the prevention of cancer.

3. In the experience of a number of leading American gynecologists, the value of the Schiller test is uncertain and doubtful.

4. The colposcope is but little used, owing to the difficulty of the interpretation of its findings.

5. At present there is no substitute for strong illumination as an aid in detecting early evidence of cervical malignancy. Biopsy and microscopic examination of any suspicious appearing lesion should be promptly performed.

6. There is general agreement that when leucoplakia of the cervix is found, it should be eradicated.

7. A more thorough and systematic training of medical students in the early diagnosis and treatment of cancer is advisable.

8. There is need for wider education of women as to the significance of abnormal menstruation and vaginal discharges. Such education of girls of high school age is suggested.

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NOTE: For lack of space it is not feasible to publish all of the papers presented at this Congress. Many of these were introductory to Round Table Discussions. A selected number is included in this issue of the JOURNAL and another group may be found in the January, 1940 number of the *Western Journal of Surgery, Obstetrics and Gynecology*. A general summary of the proceedings of the Congress is presented in Dr. F. L. Adair's article published in the October, 1939 issue of the JOURNAL, and a special summary of the obstetric papers may be found in the article by Dr. G. C. Schauffer in the present issue. Complete Proceedings of the Congress may be published at a later date by the American Committee on Maternal Welfare.

In performing the test after proper antisepsis of the vulva, the labia are widely separated and the sterile glass tubing (0.5 inch diameter and 3.5 inches long) is inserted into about one-third distance of vaginal tract. Through this tubing the dyed applicator is passed until it approaches the site near the external os where amniotic fluid should be of the greatest concentration if rupture of the membranes has occurred. Thus the glass tubing has a twofold purpose: To allow a sterile introduction of the dyed applicator high into the vaginal vault, and to obtain a correct pH reading of the vagina not affected by urine which may have trickled down over the introitus. The applicator is left in the vagina for thirty seconds, removed, and change in color is noted. Interpretations of the color changes are as follows:

Yellow	pH 5.0	} Intact membranes
Olive yellow	pH 5.5	
Olive green	pH 6.0	
Blue green	pH 6.5	} Ruptured membranes
Blue gray	pH 7.0	
Deep blue	pH 7.5	

As a rule the change in color on the applicator is complete, a change only on a portion of the cotton tip speaks for intact membranes. This is not so with the bromthymol blue indicator in which a tiny speck of green, which can easily be overlooked, occurs with the break in the bag of waters. This is one of the advantages of nitrazine dye over bromthymol blue. Any change in color of the applicator to that containing a bluish hue, whether it be blue green, blue gray, or blue black indicates a pH of 6.8 or higher which in all probability is due to a spill of the amniotic fluid into the vaginal tract. Color changes of olive green to all shades of yellow indicate a pH on the acid side due to the non-entrance of the amniotic fluid and which is the normal reaction of the vagina.

## RESULTS

The test was performed on a large number of out-patients on the Los Angeles County Maternity Service and in-patients on the Obstetrical Service of the Los Angeles County General Hospital. These patients were all at term or in labor with or without suggestive history of ruptured membranes. For comparative study and evaluation, both the nitrazine and bromthymol blue indicators were used simultaneously on all patients examined. The ultimate check-up on the actual condition of the membranes was determined by vaginal examination for the presence or absence of the bag of waters when the patient was placed on the table for delivery, or by noting when definite rupture occurred as manifested by a sudden break in the membranes and visualization and smell of the amniotic fluid. Thus the relative accuracy of the tests was determined in each case, and the results were interpreted as being true or false.

When the indicator showed a change in pH toward the alkaline side due to ruptured membranes, giving a positive result which was later verified, it was considered as a true positive. But if a positive result appeared in a patient with known intact membranes, it was classed as a false positive. Conversely, if the indicator dye did not produce any change toward the alkaline side in a case subsequently proved to have intact membranes, it was interpreted as a true negative. And if the test failed to demonstrate a change to the alkaline side in a case with definitely ruptured membranes, it was classed as falsely negative.

A total of 176 patients, approaching or in labor, were given these tests. For the nitrazine test, 97 indicated rupture of the membranes and were recorded as positive, and 79 showed intact membranes and were marked as negative. Of the 97 positive results 96 (98.9 per cent) proved to be true, and in only one case the test revealed a falsely positive outcome. Seventy-six (96.2 per cent) of the 79 negative cases turned out to be correct with three giving false results. The combined accuracy of the true positive and the true negative results was 97.7 per cent.

The purpose of this paper is to show the results of a similar test that is identical in principle, but employing a different indicator dye and some modification in technique. The indicator used was nitrazine (sodium dinitrophenylazonaphthol disulphonate) test solution which is now available on the market.

### PRINCIPLE OF THE TEST

The normal reaction of the vaginal secretions is acid. Temesvary demonstrated by colorimetric methods the pH range of the vagina in pregnant women at term to vary from 6.0 to 5.2. Using hydrogen ion electrode, Bock corroborated with similar figures. Whereas, in women with ruptured membranes the former found the pH to be 6.0 to 8.1, and the latter reported the rise in pH to be 6.8 to 8.2.

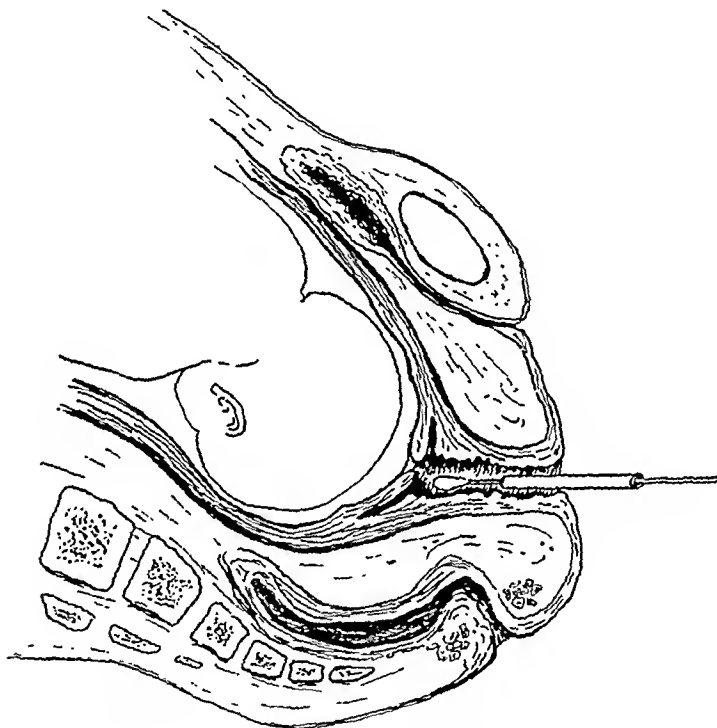


Fig. 1.—Showing position of glass tubing through which the dyed cotton applicator is inserted.

Thus the nitrazine indicator which offers the sharpest end point between 6.4 and 6.8 should be an ideal indicator for detecting any alteration in vaginal pH due to the entrance of amniotic fluid from a ruptured sac. The abrupt end point at such a narrow range is theoretically a better indicator dye to employ than bromthymol blue which changes from orange to blue green at a pH of 6.0 to 7.7.

### TECHNIQUE

Ordinary cotton applicators are dipped in nitrazine test solution and then dried. Upon evaporation the dye yields a canary yellow color with scattered streaks of green. This is the neutral point at about pH 6.6. A dyed cotton applicator and a short glass tubing, the purpose of which will be explained later, are placed in a large size test tube and stoppered with a cotton plug. This is then autoclaved. The test tube container is used purely for convenience, as it can be kept in the labor room for immediate availability or carried around as part of the doctor's equipment.

indicator was passed proved to be a valuable modification. Care must be used in its insertion, as otherwise it may be painful and injurious. It must be certain that its ends have been flamed over the Bunsen burner to smooth off its edges. It is of importance that some form of antiseptic preparation of the external genitalia be made previous to the introduction of the glass tubing. Type of antiseptic used will have no effect on this test, as the dyed cotton applicator is inserted beyond reach of any antiseptic solution. In using this sterile tubing as an aid in inserting the dyed applicator into the vaginal vault, there was not a single case of post-partum infection in those patients tested.

#### SUMMARY

1. A modification of a test to determine rupture of fetal membranes, using the principle of alteration of the vaginal pH following the rupture of membranes, is presented. The test involves the use of a new indicator dye, nitrazine (sodium dinitrophenylazonaphthol disulphonate), and a technique which is sterile and avoids the influence of urine and antiseptic solutions on the indicator dye.

2. One hundred seventy-six patients from the Los Angeles City Maternity and Obstetrical Services of the Los Angeles County General Hospital were given this test and the bromthymol blue test simultaneously, and comparative studies were made regarding their accuracy.

3. The nitrazine test was found to give greater accuracy in those patients where the membranes were not ruptured, as its percentage accuracy for true negatives was 96.2 per cent in comparison with the bromthymol blue test which was 86.6 per cent. In those patients tested with known ruptured membranes, both tests gave equally accurate results, 98.9 per cent and 97.6 per cent, respectively.

4. No post-partum infection followed any patient tested with this technique.

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**Korbulý, G.**: Contemporary Pictures of Semmelweis, Zentralbl. f. Gynäk. 62: 738, 1938.

Stimulated by an article by B. Otton (Zentralbl. f. Gynäk. 1929) in which a supposedly unknown photograph of Semmelweis was published, the author has assembled and reproduced all pictures available at present. These are documented and will be of value to the historian. Among the pictures is an oil painting of dubious authenticity, representing Semmelweis as a lad of 12 to 14 years. A copy of a photograph not previously published, and taken in 1858, is reproduced. Two little known photographs, taken in 1863 and 1864, are of interest in their demonstration of the effects of Semmelweis' struggle for recognition of his work and of the ravages of the disease from which he must have been suffering at that time. Altogether nine pictures are nicely reproduced and traced.

J. L. McKELVEY.

TABLE I. NITRAZINE TEST

NUMBER OF CASES	REACTION	TRUE	FALSE	PER CENT ACCURATE
97	Positive	96	1	98.9
79	Negative	76	3	96.2
Total 176		172	4	97.7

For the bromthymol blue test 86 of the 176 cases showed the bag of waters to be broken. Eighty-four (97.6 per cent) of these were revealed to be true later and two were false. Ninety of the cases tested with this dye indicated intact membranes, but only 76 (86.6 per cent) were verified to be true and 14 proved to be false, the combined accuracy of the true positives and the true negatives of this group being 90.9 per cent.

TABLE II. BROMTHYMOL BLUE TEST

NUMBER OF CASES	REACTION	TRUE	FALSE	PER CENT ACCURATE
86	Positive	84	2	97.6
90	Negative	76	14	86.6
Total 176		160	16	90.9

## DISCUSSION AND CONCLUSION

It is to be noted that both the nitrazine and bromthymol blue tests gave an uniformly high percentage of accuracy (98.9 per cent and 97.6 per cent, respectively) in indicating rupture of the bag of waters as manifested by their change in color of the dye. The results with the bromthymol blue tests in this research conform closely to the findings reported by King in respect to true positives (he reported 94.7 per cent). It can be certain then that a positive result in either of these tests speaks very strongly for ruptured membranes and clinically can be assumed as such.

However in those patients with intact membranes, the occurrence of false negatives was more frequent in the bromthymol blue test (14) as compared with the nitrazine test (2). And in both of the cases where false negatives occurred in the nitrazine test group, the results were likewise false with the bromthymol blue test. Thus, in general, the bromthymol blue test did not measure up to the accuracy of the nitrazine test in a good many cases. The relatively frequent occurrence of the falsely negative results with bromthymol blue test in patients having ruptured membranes perhaps may be explained. King attributes this discrepancy to insufficient amount of amniotic fluid, due to its draining off or to settling of the infant's head to prevent further flow, or to the fact that "natural vaginal acidity had reasserted itself." Due to the fact that the nitrazine test proved to be accurate in 98.9 per cent of the cases where the membranes were ruptured, this dye speaks for greater sensitivity of the nitrazine dye because of its sharper and slightly lower end point. It may be that the amount of the amniotic fluid spilled into the vaginal vault was insufficient to cause any change in the bromthymol blue dye, but sufficient to alter the hue of the nitrazine from yellow to a blue green color.

The technique of using the short glass tubing as a protective cylinder through which the sterile applicator stick with its cotton and dye in-

not fail to yield considerable valuable information concerning the metabolism of these hormones. From these ideas the present investigation evolved.

### METHODS

For the determination of chorionic gonadotropin and estrogen in the serum, 40 c.c. of venous blood are taken without any anticoagulant, the clot allowed to form, and the serum separated. Chorionic gonadotropin is extracted and assayed by the method recently described.<sup>5</sup> More animals are used than were recommended in this publication, in order to obtain a closer end point. The serum remaining after chorionic gonadotropin assay (usually 15 to 20 c.c.) is accurately measured and precipitated with about 5 volumes of ethyl alcohol for the extraction of estrogen. After standing twenty-four hours or longer, the alcohol is removed by centrifugation, the precipitate thoroughly washed twice with alcohol and twice with ether, and all solvents are combined and evaporated to dryness. The residue is taken up in normal saline solution (using a rubber policeman and frequent washings with saline) and made up to a measured volume with saline. After shaking to a smooth emulsion, aliquot portions are assayed on mature spayed female rats, following the previously described technique.<sup>7</sup> It has been found necessary to extract the serum, since the large amounts necessary to give a positive test have occasionally proved toxic. The test is not thoroughly satisfactory because the limited amount of serum does not permit as many assays as are desirable for reaching an end point. Attempts to obtain higher values for serum estrogen, such as through hydrolyzing the serum itself (by acid hydrolysis or by incubation) or through butyl alcohol extraction followed by acid hydrolysis of the evaporated extract, have been unsuccessful. The method described yields values which agree with assays on the straight serum and appears to give information of physiologic significance.

For the determination of pregnanediol and the estrogens, a twenty-four-hour specimen of urine is collected and extracted within twenty-four hours of the time of collection. It is our habit to perform a creatinine determination<sup>8</sup> on each specimen and keep a record of the twenty-four-hour creatinine output for each patient followed. Since the daily excretion of creatinine for any individual is relatively constant, any gross error in a twenty-four-hour collection can be readily detected and a value closely approximating the true twenty-four-hour volume calculated.

Sodium pregnanediol glucuronidate has been gravimetrically measured according to the method of Venning.<sup>9</sup>

An exact description of the method now employed by us for determining estrone, estriol, and "x" estrogen, i.e., estradiol, in human urine is being separately published.<sup>10</sup> Although the method of separation is not strictly quantitative, recovery experiments<sup>10</sup> have indicated that most of the potency designated as estrone, estriol, and estradiol is accountable to these three hormones, respectively. The technique of bio-assay has been described in a previous publication.<sup>7</sup> Inasmuch as our animals are standardized against crystalline estrone, estriol, and estradiol, the results below are expressed in terms of weight as well as rat units. The amount of estradiol benzoate administered is converted in the charts into milligrams of estradiol, the latter being 72 per cent of the former.

Because of the high incidence of pre-eclampsia toxemia and premature delivery in diabetic women, we have concentrated on these patients in following hormonal changes prior to clinical manifestations. Comparative assays of serum and urine from diabetic and nondiabetic pregnancies have revealed no essential difference in the chorionic gonadotropin or estrogen changes of these two groups, either throughout normal pregnancy or before and during the development of late pregnancy toxemia or premature delivery.<sup>3, 5</sup> The fact that most of the patients herein studied were diabetics, therefore, does not influence either the

# ESTROGEN AND PROGESTIN METABOLISM IN PREGNANT WOMEN\*

WITH ESPECIAL REFERENCE TO PRE-ECLAMPTIC TOXEMIA AND THE EFFECT OF HORMONE ADMINISTRATION

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AN ENDOCRINE imbalance in pre-eclamptic toxemia, eclampsia, and certain cases of premature delivery has been definitely indicated by our previous quantitative studies.<sup>1-5</sup> Our earlier investigations revealed excessive chorionic gonadotropin and low levels of estrogen in the serum and urine of patients exhibiting these disorders. Later the abnormal rise in serum chorionic gonadotropin was found to precede clinical signs by some weeks. With improved methods for extracting and separating urinary estrogens, it became possible to gain more information concerning their metabolism in women. Progesterin appeared to be necessary for their normal metabolism and utilization, and in the absence of sufficient progesterin they appeared to be more rapidly destroyed.<sup>4, 6, 7</sup> It seemed possible, therefore, that the explanation for low levels of estrogen in pre-eclamptic patients might lie in a progesterin-deficiency with a resultant increased destruction of estrogens. Preliminary studies of urinary pregnanediol, estrone, estriol, and "x" estrogen in pre-eclampsia gave evidence that a progesterin, as well as an estrogen, deficiency did follow the abnormal rise in chorionic gonadotropin and that the onset of clinical signs was accompanied by the marked shift in the distribution of urinary estrogens, which we have come to associate with a more rapid destruction due to progesterin-deficient metabolism.<sup>4</sup>

The demonstration of a typical hormonal imbalance involving an estrogen and progesterin deficiency has seemed to warrant the administration of these two substances in the hope of re-establishing a normal balance. If this were accomplished and accompanied by clinical benefit, one would have some basis for assuming that the disturbances were the direct result of some change associated with a progesterin-deficient metabolism of the estrogens. Furthermore, the quantitative determination of chorionic gonadotropin and estrogen in the serum and of estrone, estriol, estradiol, and pregnanediol in the urine, before and after the administration of large amounts of estrogen and progesterone, could

\*The Mrs. William Lowell Putnam Investigation of the Toxemias of Pregnancy, aided by a grant from the Committee for Research in Problems of Sex of the National Research Council.

†The discovery of this third estrogenic factor in urine and data concerning its physiologic significance are reported in reference 4. On Dec. 1, 1938, we submitted to Dr. E. A. Dolsy the estrone fraction from 38 liters of urine from women during labor and delivery. On Aug. 21, 1939, Dr. Dolsy informed us that he had isolated and identified dihydrotheelin (estradiol) in this material.<sup>19</sup> It seems safe to assume, therefore, that most of the nonketonic potency of estrone fractions (our so-called "x" estrogen) is accountable to estradiol.



a progestin-deficient metabolism of the estrogens is concerned in the initiation of labor, the primarily responsible change would be a failing utilization of chorionic gonadotropin for the elaboration of these steroids.

Analyses of single twenty-four-hour specimens of urine from 3 pre-eclamptic women and 3 normally pregnant at approximately the same period of gestation (thirty to thirty-eight weeks) were performed. The urines from pre-eclamptic patients were featured by low pregnanediol (an average of 31 mg. as compared with an average of 108 mg. in the normals), complete absence of estrone (as compared with an average of 1.5 mg. in the normals), high estradiol (an average of 0.2 mg. as compared with an average of 0.13 mg. in the normals), and low estriol (an average of 14 mg. as compared with an average of 39 mg. in the normals), these changes being entirely similar to those observed at the time of normal labor. Thus the same progestin-deficient metabolism of the estrogens which appears to accompany labor seems, when it occurs prematurely, to be closely associated with pre-eclampsia.

The sequence of the endocrine changes which preceded and accompanied pre-eclampsia in an untreated patient have already been published.<sup>4</sup>, Chart 5 In this case the abnormal rise in serum chorionic gonadotropin was first noted at twenty-two weeks. At twenty-eight weeks high chorionic gonadotropin was still the only demonstrable abnormality. Two and one-half weeks later, however, when urinary albumin was first noted, a marked rise in urinary estrone failed to be accompanied by a corresponding increase in estriol excretion, indicating failure in conversion of estrone to estriol, due to progestin-deficiency. Such a deficiency was borne out by a drop in urinary pregnanediol. A sudden increase in the severity of clinical signs three days later was accompanied by an equally sudden shift in the hormonal findings, namely, a drop in serum estrogen, urinary pregnanediol, and estriol, a rise in estradiol and *the complete disappearance of estrone*. It is impossible to interpret these shifts of excreted estrogen as reflecting failure of conjugation or kidney retention. The rise in urinary estradiol and the diminished serum estrogen argue against this explanation. The most satisfactory interpretation is that a failure in the conversion of estrone to estriol resulted from a decreasing elaboration of progestin and that the withdrawal of sufficient progestin-protection finally resulted in rapid destruction of estrogens, as indicated by the sudden complete disappearance of estrone.

Mrs. M. W. (Table II) had been studied by us through a previous pregnancy,\* in which pre-eclampsia had been terminated by intrauterine fetal death. The pregnancy covered in this table was very briefly summarized in 1938.† Pre-eclampsia was predicted by the rising chorionic gonadotropin and preceded by a lowered excretion of pregnanediol and all 3 estrogens. The findings are in keeping with the assumption that a failure in the utilization of chorionic gonadotropin was resulting in decreasing, rather than the normally increasing, elaboration of estrogen as well as progestin with advancing pregnancy. An unprecedented situation accompanied the onset of toxemia, the disappearance of all the urinary estrogens. This applied to 4 specimens collected during the week of December 23 to 29. On December 22 the patient had been in mild diabetic coma. We wonder if some urinary constituent associated with this incident may have either destroyed estrogens or rendered the method of hydrolysis or extraction ineffective. Of all the urines from pregnant women that we have tested for estrogens by any method, these are the only ones in which no estrogenic potency has been found. The presence of serum estrogen demonstrates that estrogen was still present in the circulation. The lowered values in the serum at this time indicate that estrogens were not being retained by the kidney. After ten days of treatment (totaling 55 mg. of estradiol benzoate and 200 mg. of progesterone) instigated by the appearance of mild clinical signs and the preceding rise in chorionic gonadotropin, estrogens re-appeared in the urine. In

\*Smith and Smith: Ref. 3, charts 5 to 8, Mrs. WWh.

†Smith and Smith: Ref. 4, paragraph 3, p. 780.

findings or the applicability of the conclusions to similar conditions in nondiabetic pregnant patients.

### EXPERIMENTAL

In Table I a fairly complete study from the third month of a normal pregnancy to delivery is recorded. The values for chorionic gonadotropin and estrogen of the serum agree with those already published. The rise in serum chorionic gonadotropin during the last four weeks has been observed in other normal pregnancies. The urinary pregnanediol falls well within the limits of the values published by Venning<sup>11</sup> (a composite curve of 210 specimens from 8 women at various stages of pregnancy). It is interesting to observe that from the twenty-fifth week on, when specimens were analyzed every two weeks, waves in the pregnanediol curve become apparent with peaks at four-week intervals and delivery when it is on the downward trend. The urinary estrone curve shows waves and troughs coincident with those of pregnanediol. Hormonal rhythms in pregnancy have been mentioned before, but their cause can at present be only surmised. Estradiol does not vary significantly until labor, when its rapid rise is accompanied by a relatively sudden decrease in estriol, which up to this time had been steadily increasing, and the complete disappearance of estrone—changes which we associate with a reduction of progestin.

TABLE I. NORMAL PREGNANCY

E. B. F., aged 33 years, grav. i, last catamenia April 18, 1938, due Jan. 23, 1939

DATE	WEEKS PREG- NANT	SERUM		URINE—24-HOUR EXCRETION						
		R.U./100 C.C.		PREG- NANE- DIOL MG.	ESTRONE		ESTRADIOL		ESTRIOL	
		C. G.†	ES- TRIN		R.U.	MG.	R.U.	MG.	R.U.	MG.
7/12-14/38	12	100	<20	9.0	50	0.033	450	0.0225	1,000	0.5
8/ 7- 8/38	16			11.7	250	0.166	1,000	0.05	4,000	2.0
9/10-11/38	21			36.0	670	0.445	1,330	0.066	8,000	4.0
10/12-13/38	25½	100	20	58.3	700	0.465	2,000	0.10	15,000	7.5
10/23-24/38	27			44.9	400	0.267	1,330	0.066	20,000	10.0
11/ 6- 7/38	29	100	33	73.2	1,330	0.89	1,330	0.066	20,000	10.0
11/20-21/38	31			65.6	400	0.267	1,200	0.06	20,000	10.0
12/ 4- 5/38	33	100	50	82.9	1,000	0.667	1,500	0.075	22,500	11.1
12/18-19/38	35	200	50	78.5	330	0.22	1,000	0.05	25,000	12.5
1/ 2- 3/39	37	200	75	99.4	1,000	0.667	1,000	0.05	53,000	26.5
1/15-16/39	39	200	75	91.7	670	0.45	1,330	0.066	60,000	30.0
1/18/39*	39½	333	50		0		4,000	0.2	20,000	10.0

Spontaneous labor followed by normal delivery.

\*Specimen collected during labor, twenty-four-hour volume calculated on basis of creatinine, not enough for pregnanediol determination.

†C. G., Chorionic gonadotropin.

The fact that a rise in serum chorionic gonadotropin has been detected during the last weeks of pregnancy, together with the observation that a deficiency of both estrogen and progestin pertains at the time of spontaneous delivery, introduces an apparent paradox, since the pregnancy gonadotropic factor characteristically stimulates the production of these 2 steroids in experimental animals. A possible interpretation, based on considerations which have been previously discussed,<sup>5</sup> is that chorionic gonadotropin is actively utilized in the elaboration of estrogen and progestin and that a failure in such utilization is reflected by increasing amounts of this hormone in the circulation.\* On this basis, if

\*We have recently had called to our attention the fact that an active utilization of chorionic gonadotropin in the placenta for the production of estrogen and progestin was suggested by Browne and Venning in 1936.<sup>20</sup>

TABLE III. DIABETES, PRE-ECLAMPSIA, HORMONAL TREATMENT

Mrs. MacD.,\* aged 36 years, gravida iii (one normal pregnancy four years before onset of diabetes, one miscarriage since onset of diabetes), last catamenia unknown. Stillbirth about 4 weeks before term

DATE	WEEKS PREG- NANT (AP. PROX.)	SERUM			URINE—24-HOUR EXCRETION						PARENTERAL INJECTIONS			CLINICAL NOTES			
		R.U./100 C.C.	PREG- DIOL MG.		ESTRONE		ESTRADIOL		ESTRIOL		ESTRA- DIOL MG.	PROGES- TERONE MG.	BLOOD PRES- SURE	ALBUMIN†		EDEMA	MISCELLANEOUS
		C. G. †			R.U.	MG.	R.U.	MG.	R.U.	MG.				QUAL.	GM. 24°		
4/10/38	12	100											110/80	0			
6/ 7/38	20	200											110/80	0			
7/15/38	25½	333+			33	0.02	133	0.007	5,000	2.5				ST		+	Nausea, abdom- inal pain, headache
7/21/38	26½	500			0		250	0.013	5,000	2.5			100/80	ST	1.5	+	Nausea, abdom- inal pain, headache
7/22/38				33													
7/29/38	27½				0		1,000	0.05	5,000	2.5	3.6 daily	10 daily	100/90	SPT	1.4	+	No subjective symptoms
8/ 4/38	28½	100	18.3	50	400	0.27	1,200	0.06	8,000	4.0		↓	100/60	SPT	0.4	±	Nausea, abdom- inal pain
8/ 9/38	29		17.7		500	0.33	1,500	0.075	8,000	4.0		↓	90/60	SPT	0.7	±	Nausea, abdom- inal pain
8/11/38	29½	100	17.0	50	300	0.20	1,300	0.065	8,000	4.0		↓	90/60	SPT	1.0		Nausea, abdom- inal pain
8/18/38	30½		24.6		800	0.54	800	0.04	13,000	6.5	↓	↓	110/70	T	5.6	+	No subjective symptoms

TABLE II. DIABETES, PRE-ECLAMPSIA, HORMONAL TREATMENT  
Mrs. M. W.,\* aged 34 years, gravida ii (pre-eclampsia and stillbirth with first pregnancy), last catamenia May 16, 1937, due Feb. 20, 1938

DATE	WEEKS PREG- NANT	SERUM				URINE—24-HOUR EXCRETION						PARENTERAL INJECTIONS		CLINICAL NOTES			
		R.U./100 C.C.		PREG- NANE- DIOL MG.	ESTRONE		ESTRADIOL		ESTRIOL		ESTRA- DIOL	PROGES- TERONE	BLOOD PRESSURE	ALB.†	EDEMA		
		C.G.†	ESTRIN		R.U.	MG.	R.U.	MG.	R.U.	MG.						MG.	MG.
9/27/37	19	50	<20	73	1,700	1.12	3,300	0.165	30,000	15.0			110/80	0	0	In diabetic coma 12/22—nausea and uterine cramps	
11/ 5/37	25	200	33	66	1,000	0.67	2,000	0.10	30,000	15.0			110/80	0	0		
11/22/37	28	200	33		600	0.40	1,400	0.07	20,000	10.0			110/80	0	0		
12/ 9/37	30½	333	33														
Admitted to hospital 12/20 because of edema and excessive gain in weight																	
12/23/37	32½	500	20	51	0		<100		<100				7.2	20	120-130/80-90	T	+
12/24/37													3.6	20	120-130/80-90	ST	0
12/25/37													3.6	20	110/70	SPT	0
12/26/37	33	333	20	60	0		<100		<100				0	20	110-120/70-90	SPT	0
12/27/37				64	0		<100		<100				7.2	20	120/80	SPT	0
12/28/37				67	0		<100		<100				3.6	20	140-110/90-80	ST	0
12/29/37		200	33				<100		<100				3.6	20	150-110/110-80	0	+
													daily	↓			
1/ 3/38													↓	↓			
1/ 4/38	34	100	66	104	500	0.335	1,000	0.05	15,000	7.5			7.2	20	140/90	ST	0
1/ 5/38				91	500	0.335	500	0.025	35,000	17.5			7.2	20	120/80	T	0
1/ 6/38													3.6	10	120/80	ST	0
1/ 7/38				85	600	0.4	2,000	0.10	30,000	15.0			3.6	10	130-110/80	0	+
1/ 8/38				92	600	0.4	1,000	0.05	40,000	20.0			3.6	10	130-140/80-90	0	0
1/ 9/38													7.2	10	120/80	SPT	0
1/10/38	35	100	100										3.6	10	110-120/80-90	SPT	0
Delivered by cesarean section. Baby lived																	

\*Ref. 18, Case 27.

†C. G., chorionic gonadotropin.

‡T, trace; ST, slightest trace; SPT, slightest possible trace.

spite of the injected estrogen, the level was lower than it had been four weeks earlier, indicating destruction as well as diminished elaboration. During this time toxemia had, if anything, become more severe. By the following week the hormonal picture was entirely normal. A little albuminuria was the only clinical sign. Elective cesarean section was performed, and a healthy baby was delivered and survived. The patient's toxemia was never more than mild, so that no committal may be made concerning any salutary effect from injections. Considering her previous history and the abnormal endocrine situation at the onset of signs, the early initiation of therapy may have warded off a more serious situation, especially since there appears to be a correlation between the clinical changes and the endocrine values.

Mrs. MacD. (Table III), who had had one miscarriage since the onset of diabetes, was first seen when approximately three months pregnant. Due to catamenial irregularity, she could not be sure that a period had preceded conception. The serum chorionic gonadotropin at about the twentieth week showed an abnormal rise. Five and one-half weeks later the patient entered the hospital with mild but definite clinical signs. The findings at this time and one week later were typical of the pre-eclamptic pattern. The indications are that both progesterin and estrogens were being elaborated in subnormal amounts for this period of gestation. The rise in estradiol between July 15 and 21, accompanied as it was by the disappearance of estrone and a failure of estriol to increase, indicates further that much of the secreted estrogen was not being properly metabolized and was being rapidly destroyed. Even after two weeks of the daily injection of 5 mg. of estradiol benzoate and 10 mg. of progesterone, there was very little increase in the urinary estrogens and pregnanediol. It would appear that this patient was destroying progesterin as well as estrogen. By September 1, after six weeks of hormone administration, estrogen metabolism appeared to be normal and the patient was symptom free, the only toxic sign being a very small amount of urinary albumin. The recrudescence of serum chorionic gonadotropin and lowered excretion of estrogens and pregnanediol a week after all injections had been omitted (September 8) supply evidence in favor of the assumption that the changes observed during injections were the result of therapy. Four days of injections, beginning on September 13, were again followed by a change in the direction of normal. By September 17 the patient was clinically well. Ten days after the discontinuation of all therapy the common diabetic accident, stillbirth, occurred a few hours after intrauterine death. Unfortunately, the patient had left the hospital after the last injection, so that we have no information concerning the clinical and endocrinologic changes from that time through the accident.

The administration of hormones to this patient was apparently inadequate for the degree of estrogen and progesterin deficiency that pertained. Yet, with prolonged treatment, there was some evidence for a more normal elaboration and metabolism of these steroids, accompanied by the disappearance of toxic signs. With toxemia as mild as hers, it might well be argued that clinical improvement would have occurred without hormone administration. Whether the injections postponed stillbirth and might have prevented it entirely had they been continued is entirely speculative.

Because of its close chemical relationship to the female sex steroids, especially progesterone, its similarity to progesterone in a number of physiologic effects,<sup>12-16</sup> and its availability in larger dosage, testosterone propionate was used as a substitute in the following 2 therapeutic trials.

Mrs. A. R. (Table IV) was a diabetic in whose previous pregnancy pre-eclampsia and stillbirth had occurred. On April 26 the patient entered the hospital with the first manifestations of toxemia and the characteristic hormonal imbalance which has been found to accompany the onset of symptoms. During the next two weeks she received 5 mg. of estradiol benzoate and 25 mg. of testosterone propionate daily. There ensued not only a depression of serum

8/20/38	50	75							3.6 alt. days ↓	10 alt. days ↓				No subjective symptoms	
8/25/38	31½		20.0	1,500	1.0	1,000	0.05	16,000	8.0	3.6 daily ↓	10 daily ↓	ST	0.9	0	No subjective symptoms
9/ 1/38	32½		0%§	2,000	1.33	2,000	0.10	20,000	10.0	0 ↓	0 ↓	100/60	0.6	0	No subjective symptoms
9/ 8/38	33½	200	23.0	500	0.33	1,500	0.075	8,000	4.0	↓	↓	110/70	0.2	+	No subjective symptoms
9/13/38										3.6 daily ↓	10 daily ↓				No subjective symptoms
9/17/38	34½	100	36.4	1,300	0.87	1,300	0.065	16,000	8.0	↓	0 ↓	100/60	0	0	No subjective symptoms
9/27/38	36									↓	↓				Stillbirth

\*Ref. 18, Case 30.

†C. G., chorionic gonadotropin.

†I, trace; ST, slight trace; SPT, slightest possible trace.

Occasionally no sodium pregnanediol glucuronide is found, presumably due to some unusual hydrolysis. This specimen had been kept cold during collection and extracted within twenty-four hours.

TABLE V. THREATENED, THEN INCIPENT, PRE-ECLAMPSIA, HORMONE ADMINISTRATION

Mrs. G. K.,\* aged 16 years, diabetic, gravida i, last catamenia Aug. 15, 1937, due May 22, 1938

DATE	WEEKS PREG- NANT	SERUM		URINE—24-HOUR EXCRETION								PARENTERAL INJECTIONS		CLINICAL NOTES		
				PREG- NANEDIOL MG.	ESTRONE		ESTRADIOL		ESTRIOL		ESTRADIOL MG.	TESTOS- TERONE PROPIONATE MG.				
		R.U.	MG.		R.U.	MG.	R.U.	MG.								
									C. G.†	ESTRIN						
1/15/38	22	100												110/60	0	0
2/15/38	26½	200												110/80	0	0
3/ 1/38	28½	333	33											124/80	0	0
3/15/38	30½	500	33	30		500	0.33	500	0.025					124/90	0	Headache
3/22/38	31½	500	33	35		700	0.47	600	0.03					118/90	0	Headache
3/23/38						2,000 (Estrone + Estradiol)										+
3/24/38				24		500 0.33	1,500 0.075									0
3/25/38	32	200	33	23		2,000 (Estrone + Estradiol)								116/50	0	
3/27/38		100	50			1,000 0.66	2,000 0.10							110/70	SPT	0
3/28/38				26		3,000 (Estrone + Estradiol)										
3/29/38	32½					4,000 (Estrone + Estradiol)										
3/31/38		100	66	34		1,500 1.0	1,500 0.075							140-150/100-120	ST/T	Headache
4/ 6/38	33½	50	75	38		2,000	1.33	2,000	0.10					110-150/80-90	SPT	0
4/ 8/38														120/80	SPT	Headache
4/10/38	34					700 0.47	1,300 0.065							120/80	SPT	0
4/14/38				29		4,000 (Estrone + Estradiol)										
4/18/38	35	100	50	23		1,000 0.66	2,000 0.10							100/60	SPT	0
4/20/38		200	50	18		5,000 (Estrone + Estradiol)										
4/26/38	36			21		1,000 0.66	3,000 0.15							100-120/70-80	SPT	Headache
4/30/38				6		500	0.33	4,000	0.20					100-120/60-80	SPT	0
5/ 3/38		200	100	6		3,000 (Estrone + Estradiol)								110/90	SPT	0
5/ 5/38	37			13		3,000 2.0	3,000 0.15							110/80	SPT	0
															0	Cesarean section. Baby lived.

\*Ref. 18, Case 28.

†C. G., chorionic gonadotropin.

†SPT, slightest possible trace.

TABLE IV. DIABETES, INCIPIENT PRE-ECLAMPSIA, HORMONAL TREATMENT

Mrs. A. R.,\* aged 34 years, gravida ii (pre-eclampsia and stillbirth with first pregnancy), last catamenia Sept. 3, 1937. Due June 10, 1938.

DATE	WEEKS PREGNANT	SERUM		URINE—24-HOUR EXCRETION								PARENTERAL INJECTIONS		CLINICAL NOTES		
		R.U./100 C.C.		PREGNANEDIOL	ESTRONE		ESTRADIOL		ESTRIOL		ESTRADIOL	TESTOSTERONE PROPIONATE	B.P.	ALB.	EDE-MA	
		C. G.†	ES-TRIN		MG.	R.U.	MG.	R.U.	M.G.	R.U.						MG.
4/26/38	33½	500	50	31	0		2,000	0.10	20,000	10.0			110/80	SPT	+	
													Gained 10 lb. in 2 weeks. Abdl. pain; headache			
4/27/38											3.6 daily	25 daily				
5/ 3/38	34½	100	100	39	1,000	0.67	5,000	0.25	30,000	15.0			110/70	SPT	0	
5/10/38	35½	50	75	64	2,500	1.68	5,000	0.25	60,000	30.0			110/60	0	0	
											↓	↓	No further weight gain			
5/11/38													Delivery by cesar-ean section; baby lived			

\*Ref. 18, Case 29.

†C. G., chorionic gonadotropin.

chorionic gonadotropin but also a rise in estrogens of both serum and urine and a shift in the distribution of urinary estrogens pointing to more conversion and less destruction—changes signifying more progestin. There was also a marked increase in urinary pregnanediol (from 31 to 64 mg. in 24 hours). Since it is unlikely that this rise could be entirely attributed to conversion of testosterone into progestin in the body, we are inclined to the opinion that it protected progestin against destruction, thereby enhancing the effectiveness of such amounts as were being elaborated. (The investigations of Pincus and Werthessen<sup>17</sup> and unpublished experiments in this laboratory have given evidence that substances chemically related to the female sex steroids enhance their action, apparently through slowing down the rate of their destruction.) Albuminuria and edema disappeared coincident with the establishment of a normal hormonal balance. A viable child was delivered by cesarean section. The patient was never sick enough to allow deductions as to the clinical effect of treatment, although, considering her previous history, an unfortunate outcome may have been averted.

In the case of Mrs. G. K. (Table V), injections were started as a preventive measure\* five weeks after the first finding of excessive serum chorionic gonadotropin and before there was any suggestion of toxemia clinically, other than headache. At the time treatment was begun serum chorionic gonadotropin had increased still further, serum estrogen had failed to rise with advancing gestation and the urinary assays reflected low levels of both progestin and estrogens. Estrone was still present, however, signifying that the striking shift in estrogen metabolism, with complete absence of urinary estrone, which has been found to

\*The assumption that an abnormal rise in serum chorionic gonadotropin during the fifth, sixth, or seventh month of pregnancy predicts later trouble is based on the study of serum chorionic gonadotropin in 173 pregnant women (31 of them diabetics).<sup>5</sup> Among the 83 cases with high chorionic gonadotropin there were no normal pregnancies, 90 per cent of these having been diagnosed as pre-eclamptic or eclamptic and 10 per cent having delivered prematurely. The incidence of premature delivery (rather than pre-eclampsia) in the high chorionic gonadotropin group was considerably higher among the diabetics (23.5 per cent) than among the nondiabetics (6 per cent).<sup>5</sup>



TABLE VI. THREATENED PRE-ECLAMPSIA OR PREMATURE DELIVERY—HORMONE ADMINISTRATION

Mrs. L. W. W., diabetic, aged 25 years, gravida ii (stillbirth at seven months two years ago), last catamenia Aug. 15, 1937, due May 22, 1938.

DATE	WEEKS PRG- NANT	SERUM		URINE—24-HOUR EXCRETION								PARENTERAL INJECTIONS		CLINICAL NOTES		
		R.U./100 C.C.	C. G.† ESTRIN	PREG- NANEDIOL MG.	ESTRONE		ESTRADIOL		ESTRIOL		ESTRA- DIOL MG.	PROGES- TERONE MG.	BLOOD PRESSURE	ALB. GM./24°	EDEMA	
					R.U.	MG.	R.U.	MG.	R.U.	MG.						
11/ 5/37	12	100		7.0		120 (Estrone + Estradiol)			400	0.2			110/60	0.278	0	
12/14/37	17	50		18.6		700 (Estrone + Estradiol)			3000	1.5			110/70	0.408	0	
1/18/38	22	100	25	0†		2,500 (Estrone + Estradiol)			10,000	5.0			110/80	0.768	0	
2/ 8/38	25	200	33													
2/28/38	28	200	33	89		1,000 (Estrone + Estradiol)			15,000	7.5			110/60	0	0	
3/14/38	30	300	33	93		1,300 0.87	2,700 0.133		10,000	5.0			120/60	0.168	0	
3/19/38		300	33	103		1,700 1.14	3,300 0.165		15,000	7.5						
											3.6 daily	10 daily				
3/20/38	31					1,700 1.14	3,300 0.165		15,000	7.5			106/80	0.132	0	
3/21/38				95		3,000 2.0	4,500 0.225		15,000	7.5						
3/22/38						2,000 1.33	3,000 0.15		15,000	7.5						
3/23/38	31½			85		5,000 (Estrone + Estradiol)			12,000	6.0						
3/27/38	32	200	50	101		1,700 1.14	3,300 0.165		20,000	10.0			110/60	0.551	0	
4/ 2/38	33			113		4,000 2.67	4,000 0.20		20,000	10.0						
4/ 6/38	33½	200	50	121		1,200 0.80	2,800 0.14		40,000	20.0			120/80	0.325	0	
															Uterine cramps	
4/ 8/38	34			100		3,500 2.33	4,000 0.20		30,000	15.0			110/80	0.121	0	
															Uterine cramps	
4/14/38		300	50	77		4,500 3.0	3,000 0.15		30,000	15.0			110-130/60-80	0.360	0	
											7.2 daily	20 daily			Uterine cramps	
4/20/38	35½	100	50	39		2,500 1.66	7,500 0.375		40,000	20.0			120-130/60-90	0.405	0	
															Uterine cramps	
4/23/38	36	100	75	89		2,500 1.66	7,500 0.375		80,000	40.0			110-120/70-80	0.474	0	
4/25/38				110		15,000 (Estrone + Estradiol)			80,000	40.0						
4/27/38						5,800 3.85	7,500 0.375		80,000	40.0			120-130/80			
4/28/38	36½								80,000	40.0			120-130/80	0.760	0	
													Cesarean section.		Baby lived	

\*Ref. 18, Case 34.

†C. G., chorionic gonadotropin.

‡See footnote Table III.

accompany clinical signs, had not yet taken place. Three days of estradiol benzoate alone (5 mg. daily) lowered the serum chorionic gonadotropin but had no effect on serum estrogen or on estrogen excretion other than to increase the estradiol. It appears that none of the injected estrogen was being converted and most of it was being destroyed. The excretion of pregnanediol decreased during this period. The giving of testosterone propionate with estradiol benzoate brought about an almost immediate change in the endocrine picture, and twelve consecutive days of this treatment were accompanied by a steady rise in serum estrogen and in urinary estrone, estriol, and pregnanediol. As in the preceding case (Table IV), the greater excretion of pregnanediol suggests that testosterone, in the amounts and for the period given, exerted a conserving influence upon progestin, thereby enhancing its action.<sup>17</sup> It is conceivable also that testosterone had a direct effect of its own, supplementing that of progestin, in the protection of the estrogens and in the conversion to estriol. On March 31, after six days of both testosterone and estradiol, the patient began showing clinical evidence of pre-eclampsia. Did this occur in spite of or due to prophylactic therapy or would it have been more severe without therapy? Clinical improvement was apparent one week later. Was it related to doubling the dose of estradiol and the ensuing further change in the hormonal balance in the direction of normal? From April 10 on, two paradoxes became evident in the chart for which we believe the continued administration of testosterone must have been responsible. The first is the alarming decrease in urinary pregnanediol. The second is the failure of total urinary estrogen to decrease strikingly and of estrone to disappear, as would be expected with such marked evidence of progestin lack. Inasmuch as continued injections of testosterone inhibit ovarian activity experimentally<sup>18</sup> and in women,<sup>12</sup> its prolonged administration, forty days, in this case would seem to have suppressed progestin production. It probably suppressed estrogen production also, but this effect would appear to be masked by the injections of estradiol and possibly testosterone's protective influence against estrogen destruction. Furthermore, testosterone was apparently fairly satisfactorily substituting for progestin in the conversion of estrone to estriol; in other words, it was maintaining a proper metabolism of the estrogens. During this period gestation progressed essentially normally and was terminated by elective cesarean section. The infant did well. In this case also no conclusions may be drawn as to the clinical effect of hormone administration, except that it did no obvious harm. Considering the fact that the patient was a juvenile diabetic and a primigravida, whose serum chorionic gonadotropin increased abnormally in the second trimester and who had incipient toxemia clinically for a few days, we are inclined to think that treatment may have prevented an accident to mother and/or child.

Because of its apparent inhibitive influence on the output of progestin when given for more than two weeks, we have avoided, at least for the present, the use of testosterone in further clinical trials. Moreover, it might be potentially harmful to fetus and mother in large dosage, because of its androgenic nature, although there was no evidence of such an effect in the case just reviewed.

Mrs. L. W. W. (Table VI), a diabetic since early childhood, was also treated before the development of any clinical evidence of toxemia on the basis of an abnormal rise in serum chorionic gonadotropin late in the sixth month (see footnote, page 413). Her first pregnancy had terminated in a stillbirth at seven months. At the time injections were started, the only demonstrable abnormality, aside from the excessive chorionic gonadotropin, was the fact that there had been no appreciable increase in estrogen excretion for eight weeks. Toward the end of a seventeen-day period of daily injections of estradiol benzoate (5 mg. daily) and progesterone, there was an increased excretion of pregnanediol and a good increase in estriol. Serum chorionic gonadotropin was still high, however,

TABLE VII. NONDIABETIC, PRE-ECLAMPSIA, HORMONE ADMINISTRATION  
Mrs. R. M., aged 26 years, gravida i, last catamenia April 25, 1938, due Jan. 31, 1939.

DATE	WEEKS PREG- NANT	SERUM		URINE—24-HOUR EXCRETION						PARENTERAL INJECTIONS		CLINICAL NOTES					
				PREG- NANE- DIOL MG.	ESTRONE		ESTRADIOL		ESTRIOL		ESTRA- DIOL MG.	PRO- GES- TE- RONE MG.	BLOOD PRESSURE	ALBUMIN		EDE- MA	MISCELLANEOUS
		R.U.	MG.		R.U.	MG.	R.U.	MG.	R.U.	MG.				QUAL.	GM. 24°		
		C. G. *	ES- TRIN														
12/29/38																	Weight 152½ lb.
1/ 5/39	36½	500	33											0	T	++	Weight 160 lb.
1/11/39														T		0	After 1 wk. MgSO <sub>4</sub> + water and salt restriction
1/12/39	37½	500	33	76.4	0	2,700	0.13	20,000	10.0					LT		0	MgSO <sub>4</sub> reduced.
1/13/39											7.2 daily	50 daily					Water intake increased to 2,000 c.c. daily —to delivery
1/14/39				81.0	0	10,000	0.50	4,000	2.0					T		0	
1/15/39														T		0	
1/16/39				88.6	6,700	4.45	13,300	0.66	13,300	6.6				T		0	
1/17/39														T		0	
1/18/39				107.0	6,700	4.45	13,300	0.66	15,000	7.5				T		0	
1/19/39														T		0	
1/20/39	38½													ST		0	
1/21/39														ST/T		0	
1/22/39		50	100	95.0	6,700	4.45	13,300	0.66	53,000	26.5				ST		0	
1/23/39																	
1/24/39				101.0	1,300	0.86	4,000	0.20	40,000	20.0				ST/T		0	
1/25/39														T		0	
1/26/39	39½	100	50	60.0	3,400	2.25	6,600	0.33	13,300	6.6				T		+	Castor oil + enema in P.M.
1/27/39		200	<33		2,000	1.34	8,000	0.40	10,000	5.0				LT		++	Labor and deliv- ery. Baby lived

\*C. G., chorionic gonadotropin.

†T, trace; ST, slight trace; LT, light trace.

and serum estrogen had not been augmented as much as would have been anticipated. In Table V it is observed that 5 mg. of estradiol benzoate were barely adequate for depressing serum chorionic gonadotropin. The omission of estradiol injections for eight days because of uterine cramps was followed, not only by a rise in serum chorionic gonadotropin, but also by a lowering of urinary pregnanediol and reduced conversion of estrone to estriol, despite the fact that progestin-administration had been doubled. (Incidentally, uterine cramps became more severe.) These observations carry the important implication that parenterally-introduced progestin alone is no more effective than estrogen alone in re-establishing a normal balance once the progestin-deficient metabolism of the estrogens has become established. It appears that adequate estrogen is required for the proper metabolism of progestin (through protecting it from destruction and aiding its conversion to pregnanediol), just as progesterone protects estrogen and facilitates estrone to estriol conversion. The fact that the omission of estradiol resulted in such marked hormonal changes implies that the previous amounts of estrogen had been barely adequate, and that, had the patient received no injections, a progressive imbalance might have occurred. These points are emphasized by the shifts consequent upon the administration of estradiol in double dosage as well as progesterone—normal chorionic gonadotropin, increased serum estrogen and greater urinary pregnanediol and estriol. Although coincident with this establishment of a normal balance, uterine cramps ceased, no committal can be made as to clinical benefit in this case.

Mrs. R. M. (Table VII) had not been followed by us prior to the onset of pre-eclampsia. On January 5 blood was taken for assay, the patient having gained seven and one-half pounds in one week and in that time having developed edema, albuminuria, and an elevated blood pressure. Serum chorionic gonadotropin was high and serum estrogen low. One week of magnesium sulphate catharsis and water and salt restriction reduced the edema but had no effect on blood pressure or albuminuria. A twenty-four-hour urine before the initiation of hormonal therapy contained considerably less estriol than is normal for the last month of pregnancy and no estrone. Pregnanediol excretion was within the limits of normal, but an actual deficiency of progestin was nevertheless indicated if our hypothesis is correct that the proper metabolism of the estrogens is dependent upon sufficient progestin. Furthermore, it seems probable that both pregnanediol and estrogen excretion were rapidly decreasing when injections were started. This is indicated by the urinary findings during the first days of treatment, namely, the small increments in pregnanediol, the drop in estriol, and the fact that the only increase in urinary estrogen was in estradiol, the administered hormone. Eight days of treatment were followed by the establishment of a normal estrogen and progestin balance and unquestionable clinical improvement. Neither of these changes was definitely apparent until after the sixth day of treatment. On the third day after injections were stopped the urinary assays still revealed a normal metabolism of the hormones, although the estrogens had dropped to a lower level. The only clinical change was a slight rise in blood pressure. By the fourth day without injections, however, albuminuria had increased and edema was present. Hormone quantification covering the next two days revealed elevated serum chorionic gonadotropin, a falling off of serum estrogen and changes in the urinary constituents which reflected decreased conversion and greater destruction of estrogens due to progestin-deficit. Pregnanediol and total estrogens were lower at this time than they had been two weeks earlier, due probably to decreasing elaboration as well as greater destruction. The patient's signs became more severe and labor was induced.

This case, in which clinical and endocrine changes are so closely related, supplies our most persuasive evidence that a progestin-deficient metabolism of the estrogens is directly concerned in pre-eclampsia. It also is the only case in which toxemia was sufficiently pronounced to warrant the conclusion that amelioration resulted from therapy with

It seems quite likely that conversion to pregnanediol may represent physiologic utilization of progestin, just as the estrone to estriol conversion appears to play an important part in the utilization of estrogens. Administration of progesterone without a commensurate recovery from the urine of pregnanediol would suggest inadequate physiologic utilization as well as destruction. The fact that injection of progesterone alone results in less pregnanediol excretion and less estrone to estriol conversion than follows the injection of progesterone and estrogen (see Table VI) indicates that estrogen facilitates the conversion of progestin to pregnanediol and prevents destruction just as progestin facilitates estrone to estriol conversion and prevents estrogen destruction. These metabolic considerations are entirely in accord with the many experimental studies which have shown the complementary effect of estrogen and progestin on one another in their physiologic activities.

One of the questions which our studies have thus far failed to answer is how much of a given decrease of estrogen and progestin is due to incomplete metabolism with destruction and how much to reduced elaboration. Any deficiency which precedes the marked change in the partition of urinary estrogens which accompanies the onset of clinical signs is presumably accountable to decreasing elaboration. The suggestion that chorionic gonadotropin is utilized in the production of these steroids and that its abnormal rise signifies failure of such utilization is proposed merely as a working hypothesis. Observations commented upon in the presentation of results seem to support this hypothesis. Once the deficiency of progestin and estrogen is established, the destructive mechanism probably accounts largely for the abnormally low values as well as the deranged metabolism observed when toxemia is present. That the deranged metabolism is associated with rapid destruction is well demonstrated by the failure, after hormone administration, to find any immediate increases, in serum or urine, commensurate with the amounts introduced. Continued injections, however, have been followed not only by a more normal metabolism of estrogen and progestin but also by less rapid destruction, as indicated by the greater recovery of the injected hormones.

In fact, it will be observed that the prolonged administration of these substances has been followed in most instances by a greater recovery of urinary estrogen and pregnanediol than accountable to the materials administered. Greater elaboration of estrogen and progestin with advancing pregnancy is, of course, to be expected under normal conditions. There is considerable evidence in the data presented, however, that the reverse situation follows an abnormal rise in serum chorionic gonadotropin after the fifth month. The lowered serum chorionic gonadotropin after hormone administration together with the evidence for increased elaboration of estrogen and progestin upon prolonged treatment, suggests a more efficient utilization of chorionic gonadotropin because of the injected steroids.

In the 2 cases in which testosterone propionate had been substituted for progesterone, a number of interesting possibilities were revealed concerning the effect of this hormone upon estrogen and progestin metabolism. That estrogens were being more completely metabolized and less rapidly destroyed, when testosterone was given together with estradiol, than when estradiol alone was administered, was definitely shown. During the first two weeks of therapy this appeared to be the result of a higher level of progestin, due either to more elaboration or less destruction of progestin because of the injected testosterone. The continued administration of testosterone was accompanied by a marked falling off of urinary pregnanediol, but by evidence, based on the amounts and partition of urinary estrogens, for a continued satisfactory metabolism and utilization of the estrogens. From these observations it would appear that testosterone has a direct effect similar to that of progestin upon estrogen metabolism, that it may protect progestin as well as estrogen against destruction, but that its prolonged administration suppresses the elaboration of progestin (and probably estrogen also, an effect which would have been masked in these 2 cases by the parenterally-introduced estrogen). These properties of testosterone may well explain its apparent efficacy in the treatment of such conditions as functional flowing.<sup>16</sup>

The results reported establish pretty conclusively that a progestin and estrogen deficiency pertains in late pregnancy toxemia and accounts for the

large but perhaps still barely adequate doses of hormones. This conclusion is confirmed by the recrudescence of toxemia on the cessation of treatment.

#### DISCUSSION AND SUMMARY

The previously published hypothesis<sup>4</sup> concerning the metabolism of estrogens in women involves the assumption that estradiol is the primary estrogen. Experimental results<sup>4, 6, 7</sup> have indicated that estradiol is convertible into estrone, this reaction being reversible, and that estrone is convertible into estriol, this reaction being irreversible and greatly facilitated by the action of progestin. Progestin has also been found to protect estrogens against destruction. The above hypothesis has been considerably strengthened and enlarged upon by the data herein presented.

Throughout these studies of pregnant women progestin has appeared to facilitate the utilization and metabolism of the estrogens through enhancing conversion to estriol and diminishing destruction. The most convincing evidence for this effect of progestin is found in the following: administration of estradiol benzoate alone brings about very little increase in excretion of estrogen and most of that in the estradiol fraction. When progesterone and estradiol benzoate are given, estrogen excretion is further augmented and most of the increase is found in the estriol fraction.

Estradiol is usually found amplified at times when total estrogen is lowered, i.e., when there is greater destruction associated with less conversion of estrone to estriol. The data are in keeping with the assumption that this factor is an estrone-precursor and that the estradiol to estrone reaction is a reversible one, the rate and direction of which are dependent (law of mass action) upon the rate of the irreversible estrone to estriol conversion. The sudden disappearance of estrone from the urine, in the face of continued or increased excretion of estradiol, has been taken to signify reversal of the estradiol to estrone reaction and more rapid destruction of all the estrogens. In this situation, which, in pregnancy, has been encountered only at spontaneous labor and at the onset of clinical signs in toxemia, estriol is still found in the urine, although in reduced amounts. Since estriol is probably formed from estrone, our only explanation for the disappearance of the latter is that, being chemically more labile than estriol and ordinarily present in much smaller amounts, any of it which escapes destruction and is not converted to estriol or back to estradiol is too little to be demonstrable. The fact that estriol is always found in pregnancy urine carries the implication that progestin is never completely absent.

That low values for urinary estrone and estriol may be accountable to renal retention seems to us untenable, both because of the failure to find a concomitant increase of serum estrogen and because a selective kidney retention as regards estrone and estriol and not estradiol seems most unlikely. There is considerable evidence in the data presented that low values for estrogens are not entirely due to decreased conversion and more rapid destruction, but that this finding is partly accountable to a decreased elaboration of estrogen as well as progestin.

Whether the urinary values for sodium pregnanediol glucuronide may be accepted as an accurate gauge of progestin elaboration is open to question. Since this substance is measured in its combined form, a failure of conjugation or some unusual hydrolysis after it had passed the kidney tubules might account for low values. This latter possibility has been exemplified by the occasional absence of sodium pregnanediol glucuronide in the urine of a woman whose excretion of this material was otherwise following a consistent curve (Tables III and VI). Low levels of pregnanediol from failure of conjugation or kidney retention in pre-eclampsia may be ruled out, since an actual deficiency of progestin is reflected by the distribution of the urinary estrogens. Aside from decreased production of progestin, there are two other possible causes for low urinary pregnanediol glucuronide: (1) failure of conversion of progestin to pregnanediol and (2) destruction of secreted hormone.

tinued for at least six days before any effect upon the hormonal or clinical picture can be expected. In fulminating pre-eclampsia such a delay is not justifiable. (3) The indications are that in cases of greater severity than any herein reported, in which estrogen and progestin destruction may be even more rapid, replacement therapy would be of no avail.

The principal value of the data presented lies in the added light which has been shed upon hormonal interrelationships in pregnant women and in the intimation that the primary etiology of pre-eclampsia, eclampsia, and certain cases of premature delivery may be associated with the premature development of an hormonal situation entirely similar to that which precedes normal delivery.

#### ADDENDUM

Since this paper was submitted for publication, 11 additional cases of pre-eclampsia have been studied; only 3 of them are diabetic. All of the 8 nondiabetic patients were exhibiting more pronounced toxic signs than any of the cases reported above, and in each, the urinary findings reflected a marked deficiency, together with the characteristically abnormal metabolism of estrogen and progestin. Five of them received estrogen and progestin (10 mg. estradiol benzoate and 30 to 50 mg. progesterone daily). Two showed definite clinical improvement and a more normal steroid metabolism during hormone administration, although neither of them was "cured." The other three patients, one with severe fulminating pre-eclampsia and two in whom clinical manifestations had been of four to six weeks' duration before treatment, were only temporarily benefited and then gradually became worse in spite of continued hormone administration. In both untreated and treated cases, the clinical and hormonal changes ran parallel. The data covering these patients will be published later.

The study of the diabetic cases in this report was facilitated through the essential and deeply appreciated cooperation of Dr. Priscilla White of the George F. Baker Clinic of the New England Deaconess Hospital, Boston, who followed our specifications in the administration of the materials used in therapeutic trials, supervised the collection of specimens and supplied us with clinical data. These same cases are included in a clinical study by her and others.<sup>18</sup> To Dr. Weston Sewall, Boston, we are indebted for helping us to acquire the data in Table VII. The Schering Corporation, through the cooperation of Dr. Erwin Schwenk, supplied the large quantities of hormones used, some of them specially prepared. Miss Sara Schiller gave much necessary technical assistance.

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deranged metabolism of these 2 steroids which is found to accompany the onset of clinical signs. They also demonstrate that a more normal endocrine balance may be accomplished by replacement therapy, provided injections are started sufficiently early in the course of the disturbance, are given in large amounts and continued for a fairly prolonged period, at least one week. Interruption or discontinuation of therapy has been followed by a reversal of the hormone changes. In none of the treated patients, except for Mrs. R. M. (Table VII), were clinical signs sufficiently severe to exclude the possibility that clinical improvement might have occurred without therapy. On the other hand, there appears to be a correlation between clinical and hormonal changes. In the case of Mrs. R. M. (Table VII), such a correlation was especially apparent and the evidence in this case alone is perhaps sufficient to warrant the conclusion that some alteration associated with a deranged metabolism of estrogen and progesterin due to a deficiency of both is directly concerned in the clinical signs of pre-eclampsia. The fact that an entirely similar hormonal picture is found at the time of normal delivery sheds some light on the mechanism of spontaneous labor and leads us to wonder why premature delivery, at the time toxic signs first appear, is not as common among nondiabetics as it seems to be among diabetics.

### CONCLUSIONS

A rise in the gonadotropic potency of the serum after the fifth month of pregnancy is followed by a decreasing production of progesterin and of estrogen. Such a phenomenon may reflect a decreasing utilization of the pregnancy gonadotropic factor for the elaboration of estrogen and progesterin. The deficiency of these 2 steroids results in a deranged metabolism of both, involving less complete conversion and utilization and more rapid destruction. Such a shift in steroid metabolism pertains at the onset of normal labor. When this change occurs prior to term, it is accompanied by the clinical signs of pre-eclampsia (or by premature delivery).

Because of the more rapid destruction which accompanies the mutual deficiency of progesterin and estrogen, and because of the fact that each of them, in adequate amounts, is required for the proper metabolism of the other, a re-establishment of a normal hormonal balance by replacement therapy can only be accomplished by the continued injection of both of them in large amounts. There is evidence that clinical improvement accompanies the establishment of a normal balance.

Testosterone propionate has an effect similar to that of progesterin upon the metabolism of the estrogens. It also appears to protect both estrogen and progesterin against destruction. It is perhaps not a satisfactory substitute for progesterin in pre-eclampsia, however, because its prolonged administration apparently suppresses the elaboration of progesterin (and possibly estrogen) and may have other undesirable effects due to its androgenic nature.

The administration of progesterin and estrogen as a therapeutic measure\* in pre-eclampsia is as yet of very limited clinical value for three reasons: (1) the large amounts required are not commercially available in sufficiently concentrated form and are still too costly; (2) in the amounts and kinds administered in this study, injections must be con-

\*This form of therapy has appeared to reduce infant mortality in a small series of diabetic pregnancies treated at our institution at the New England Deaconess Hospital.<sup>18</sup> The hormone assays on most of these patients were performed by us and treatment advised only in those showing an abnormal rise in serum chorionic gonadotropin between the fifth and seventh months.



It would seem that the results of the extraperitoneal operations, with uterus and the function of childbirth conserved for the patient, should relegate cesarean-hysterectomy to the group of out-dated and obsolete operations except in unusual instances.

The extraperitoneal operation of Latzko is not simple, neither is it too difficult for the obstetric surgeon. It does contain a number of real and potential dangers, however, which vitiate to some extent and in some hands, its acknowledged value.

The lateral dissection itself is not simple, and one without sufficient experience may encounter unexpected difficulties. Variations in degree of dextrorotation of the uterus, close proximity of the ureter with marked dextrorotation, varicosities in the broad ligament and bladder base, low and very adherent peritoneal fold, the relatively small exposure in deep pelves and in fat women, the likelihood of peritoneal laceration in extracting large babies, introduce threatening factors in the performance of any Latzko procedure.

Theoretically, the most highly desirable extraperitoneal operation would (1) avoid opening the peritoneum during or after extraction of the baby, (2) avoid injury to the ureters, (3) avoid injury to the bladder, (4) avoid the easily infected cellular tissue lateral to the bladder, (5) give full view of the separated tissue and the operative field, (6) give ample room for extracting any size fetus, (7) permit careful two-layer closure of uterus and thorough inspection for venous bleeding, if any, (8) leave the patient with a good uterine and abdominal wall.

The author considered the direct supravescical approach, with certain modifications, best suited to meet these desiderata. Operators for radical removal of the bladder have long denied, yet seemingly it is an accepted obstetric belief, that the supravescical peritoneum is very adherent. The peritoneum is extremely adherent to the perivesical fascia but both as a unit are separable from the bladder. It is then possible to identify the perivesical and periuterine portions of the fascia endopelvina, and by incising them in given manners and planes, permit adequate separation of the bladder from the uterus.

Once accomplished, these two maneuvers should permit the bladder to be dropped down and forward from the lower uterine segment, and the separated supravescical peritoneum with attached fascia and the periuterine fascia and peritoneum held upward, thus giving a large exposure of the lower uterine segment.

The ease with which this is done is dependent upon known and easily demonstrable changes in the pelvic structures induced by pregnancy. The uterine growth and displacement out of the pelvis loosens the peritoneal attachment to the lower uterine segment, whence it is separated with amazing ease. The lifting of the vesicouterine plica bares the bladder of peritoneum except for its posterosuperior surface, a spread of about 3 to 4 cm. in the collapsed state. The distention of the lower segment of the uterus and the thinning of the pericervical and pubovesical ligaments of the fascia endopelvina in the last trimester of pregnancy permit easy separation of the posterior surface of the bladder from the uterus and enables one to carry it far down and forward.

# SUPRAVESICAL EXTRAPERITONEAL CESAREAN SECTION\*

## PRESENTATION OF A NEW TECHNIQUE

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THE purpose of this paper is to present a new technique for a true extraperitoneal performance of cesarean section. To avoid confusion in terms and to clarify the issues involved, the present-day cesarean techniques are first considered. I would recall the early need for extraperitoneal operation, based upon the inadequate asepsis and antisepsis, poor or no anesthesia, imperfect technique, and other important factors in former days; likewise, the high incidence of neglected cases, with previous unsuccessful attempts at vaginal delivery. In the present century, and more especially the past twenty-five years, the fruits of bacteriology, anatomy, and surgical research have made all abdominal operations, including cesarean sections, incomparably safer than before. The advances in all fields have effected such reductions in mortality and morbidity that cesarean section mortality in good clinics does not exceed 5 per cent as compared to 50 to 100 per cent in the nineteenth century. The question might therefore be asked: Are true extraperitoneal cesarean sections needed today? Before arbitrarily answering, a consideration of the purpose of the operation is in order.

The low transperitoneal retrovesical operation is by all standards safer and better than the low segment Sanger incision, but it cannot and does not prevent peritoneal contamination. Cesarean hysterectomy cannot conceivably be better than a true extraperitoneal operation except in the 15 to 20 per cent group of fatal sepsis through uterine wall and lymphatics, and even in this group one may question its effectiveness. It is obvious that, if its indications are broad, a large majority of the operations are needless sacrifice of uteri, while, if the operation is long delayed, it will be ineffective for the very indication it is presumed to satisfy. The indication for a true extraperitoneal operation is therefore the probable or actual existence of intrauterine infection. If properly done, it should largely remove peritonitis as a cause of postoperative mortality, and at the same time it conserves the uterus.

It logically follows that the operation should be done in cases of reasonable doubt, if its technical safety and the results obtained in any appreciable series can be demonstrated as not more hazardous than other cesarean techniques. The results obtained with the Latzko procedure by Burns, Steele, Norton and others give a mortality for a group of 151 cases as 5.3 per cent. This figure, considering the status of the majority of cases at the time of operation, compares very favorably with the transperitoneal operations.

\*Presented before the New York Obstetrical Society, January 10, 1939, and in essentially the same form before the Brooklyn Gynecological Society, April 7, 1939, the Boston Obstetrical Society, March 21, 1939, and the New York Academy of Medicine, May 23, 1939.

depth of the bladder effacement, and cultures made from the amniotic fluid and uterine cavity. With a bandage scissors, a crescentic incision is then carried in either direction, first to left, then to right, the ends curved upward, and reaching 1 to 1½ inches above the apex of the crescent.

In vertex presentations, one blade of a forceps is slipped into place above the symphysis and used as a vectis to lift the head out of the pelvis. The head is delivered through the incision by use of the vectis and suprafundal pressure. The edges of the incision are seized with Allis or "T"-clamps, using four in all.

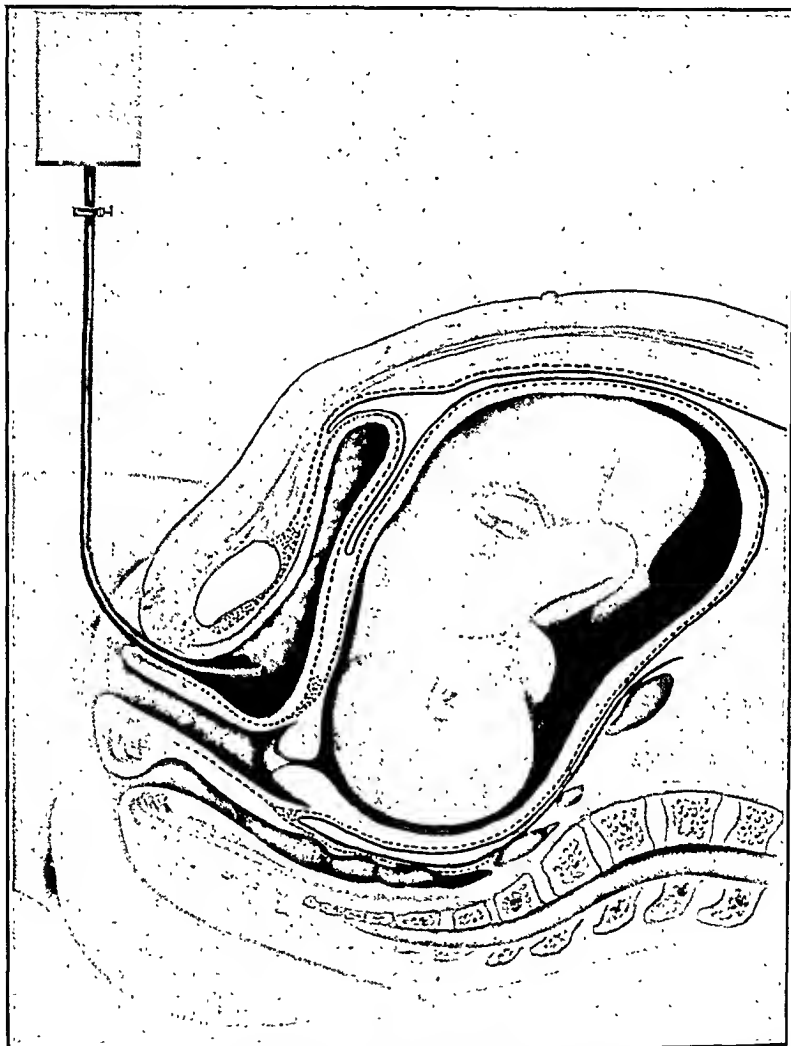


Fig. 1.—Diagrammatic cross section, showing perivesical and periuterine fascia and peritoneal relations. Outline of partially distended bladder shown, indicating depth of uterovesical peritoneal plica.

Suction clears the wound area. A running suture begins at the left side of the incision with stitches placed closely after the placenta is manually removed with its membranes. The second layer of sutures is a running Lembert, or Cushing, completely inverting the first, so that any wound infection will tend to discharge into the cervical segment and be cast out with the lochia.

The operative area is thoroughly cleaned, inspected for any venous ooze, and the bladder refilled to check for damage. It is then emptied, and the retrovesical space drained with rubber tissue. The transversalis fascia is sutured with interrupted chromic No. 1, and the rectus fascia with continuous chromic No. 2. Interrupted silk retention sutures and clips are used on the skin.

In actual dissection of the bladder peritoneum, the subperitoneal tissue is carried away with it, conserving its vitality and facilitating its post-operative reattachment.

If the uterus now be incised transversely, in a crescentic manner with apex downward, several effects are obtained. The curved incision, acting as the "diameter for the circular birth opening in the uterus," is more effective than a straight line between its terminal points could possibly be, for the longer line or diameter allows a larger "birth circle" in the elastic uterus. Again, by curving upward, it effectively escapes the uterine end of the broad ligaments, whether or not they are venously engorged. The easily infected cellular tissue low down at the bladder supports is avoided. Nothing is cut that is not under direct vision. The uterine arteries are avoided and the ureters cannot possibly be jeopardized, even in cases of marked dextrorotation of the uterus. The incision is kept for most of its length well within that section of the uterus where fibrous muscular ratio favors scar placement. Past experience with the incision in transperitoneal operations shows it to be an excellent one, and by all comparative data, the best site for a uterine scar.

#### DESCRIPTION OF OPERATION

With these concepts in mind, the author proposed and performed the following operation:

Patient is prepared vaginally. An indwelling catheter is placed in the bladder and connected with an irrigator containing sterile aqueous solution of methylene blue.

A left paramedian "trap door" incision is made in the abdomen from pubes to 1 inch below the umbilicus. In fat women and where desired, the Pfannenstiel incision is chosen. The bladder is distended with 200 c.c. or more of solution. Transversalis fascia is incised vertically. The laminated perivesical fascia is incised down to bladder muscularis for 1 inch about two-thirds of the distance to the bladder fundus. The vesical vessels are seen lying upon it as the handle of a scalpel is inserted and the fascia freed, and then incised transversely over the top and left of the bladder fundus in a "T" fashion. This permits the parietal peritoneum above the bladder to be carried up with the fascia, and the bladder separation begun. (The bladder is then drawn downward and the vesicouterine plica sought. The bladder is now emptied.) This is usually located at the left side of the bladder near the top, where the plica is most easily seen and the depth is less, due to the usual dextrorotation of the uterus. The areola tissue in this area is easily separated by holding the bladder down with a sponge and separating bluntly. Care must be taken to seek and identify the fold of peritoneum which in every case looks exactly like a hernial sac. When the "sac" is seen, direct division of the loose areolar tissue is permitted and (with the operator on the patient's right side) the finger of the left hand insinuated under it. Behind the finger is the periterine fascia and the uterus, above the peritoneal fold, below the perivesical fascia at the back of the bladder and resting on the finger is the peritoneal fold of the uterovesical pouch. The integrity of the last must be maintained. This is the most important part of the entire operation.

By sharp dissection with knife tip and under direct vision it is now possible to free the vesicouterine plica from the posterior surface of the bladder. This involves incising again the perivesical fascia, but this time near the uterovesical junction. This permits the bladder to be dropped down and forward in back of the pubis. Any bleeding from retrovesical veins is directly visible and points are ligated with No. 00 plain catgut. A large curved angle retractor holds the bladder downward, and two Richardson's are used for lateral retraction. A central "nick" is made through the now well-exposed lower uterine segment about  $1\frac{1}{2}$  inches above the

Certain minor variations in technique may be employed, depending upon the patient and the operator. The amount of bladder fill may vary from none to 400 or 500 c.c. Fascial identification is simpler with a well-filled bladder, but fascial dissection is easier and quicker with the bladder empty. The inserted catheter serves as a guide to bladder outline.

To briefly review the manner of fascial incisions, it is seen that first the transversalis fascia is incised. Then the perivesical fascia is divided as it covers the



Fig. 4.—Approach over left top of bladder. Collapsed bladder drawn downward with gauze, the peritoneofascial tissue above "T"-incision drawn upward. Hernia-like margin of vesicouterine plica sought behind left top of bladder. Lower finger on bladder, upper on hernialike peritoneal margin, and between is noted lower anterior segment of uterus.



Fig. 5.—Plica with attached fascia partially lifted from anterior surface of uterus. Attachment of fascia to bladder fundus shown.

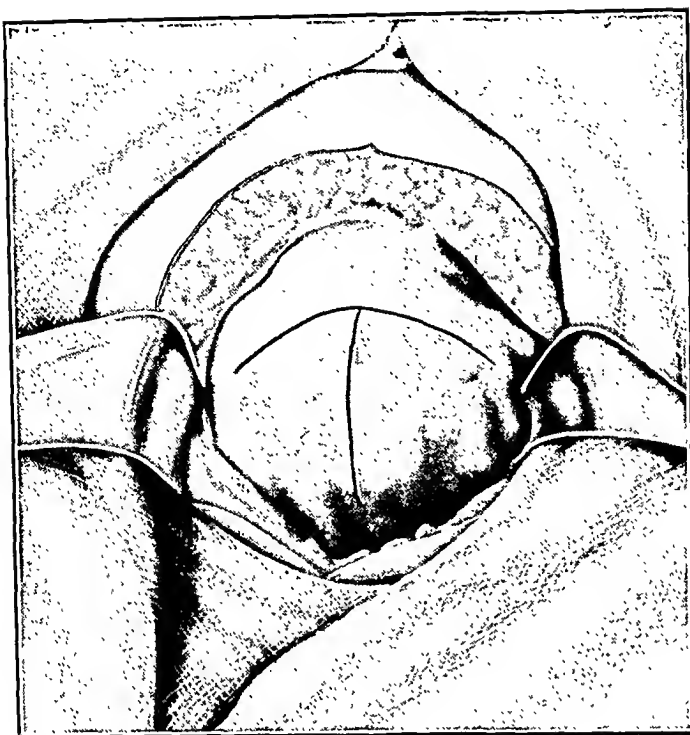


Fig. 2.—Distended bladder covered by perivesical fascia and the transversalis fascia below the parietovesical peritoneal fold. A "T"-shaped fascial incision made as indicated, down to the muscularis. This is determined by its character and by the vesical blood vessels lying between fascia and bladder muscularis. Dissection is done with knife, handle, and curved scissors.



Fig. 3.—Fascia above top of "T"-incision dissected upward with finger, scalpel handle, and gauze. This denudes anterior and upper part of the bladder of its fascia and overlying peritoneum.

fundal portion of the bladder near the parietovesical peritoneal reflection. After separation of this, especially over the left upper bladder angle, the same layer is again incised posteriorly to expose the fascia covering the lower uterine segment. Thus the bladder is "denuded" of its fascia which remains attached to the peritoneum, from bladder fundus to the uterovesical pouch. This permits the peritoneum to be freely and easily lifted and the bladder dropped far down. Incision of the uterine fascia over the lower segment occasionally is needed to increase the mobility of the uterine peritoneum.

*Postoperative Care.*—The drain is left in 2 to 5 days, depending upon the infectivity of the case. The bladder catheter is left in two days. Prostigmin (P) is given every 4 hours for 24 hours; then every 6 hours for 24 hours. Spinal anesthesia is the anesthesia of choice, and patients are permitted fluids immediately, soft diet in 24 hours and regular diet in 48 hours, barring complications. Intravenous glucose with or without insulin and blood transfusions are freely resorted to where there is the slightest indication.



Fig. 8.—Retractors hold bladder down, peritoneofascial flap upward and also placed for adequate lateral exposure. Field shown is lower uterine segment. Type and location of uterine incision indicated.

### RESULTS IN 32 CASES

Thirty-two patients have been operated upon by the technique described above. Two operators performed 27 out of the 32 operations listed.

Twenty-four of the patients were primiparas, 6 were multiparas. Of the latter, 3 had previous cesarean sections. There were no maternal deaths among the 32 cases.

There was one fetal death. This patient, a para iv, had ruptured membranes 71 hours and had been in labor 82 hours. Although her past obstetric experiences had been satisfactory, a pelvic operation of unknown type had preceded this pregnancy. The cervix became neither dilated beyond 2 fingers nor effaced. Extra-peritoneal section was chosen because of prolonged labor and ruptured membranes, temperature of 102.4° F. and very foul vaginal discharge. The fetal heart was questionably present before operation, but the baby was dead when extracted. The mother had a foul wound infection at the drain site, and was not discharged until completely well and healed on the twenty-third postoperative day.

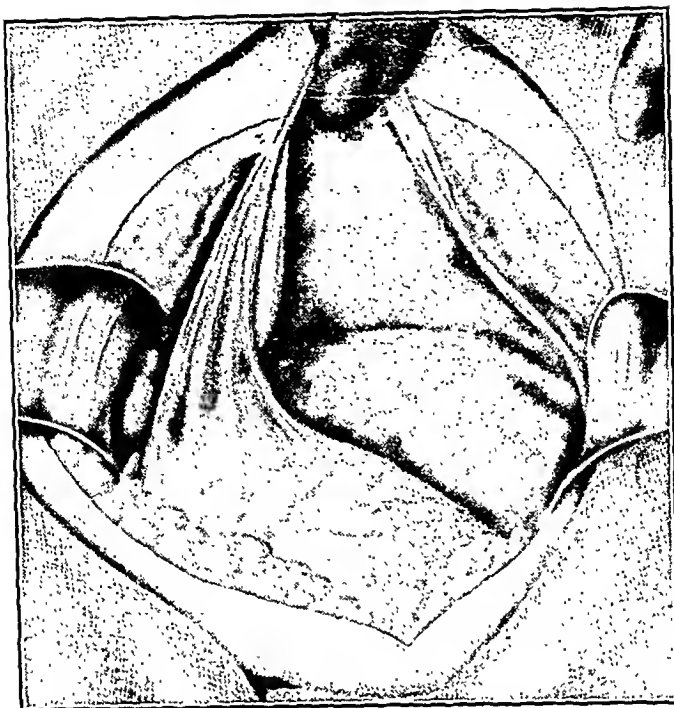


Fig. 6.—Plica well dislocated from bladder by sharp dissection, exposing larger section of uterus.

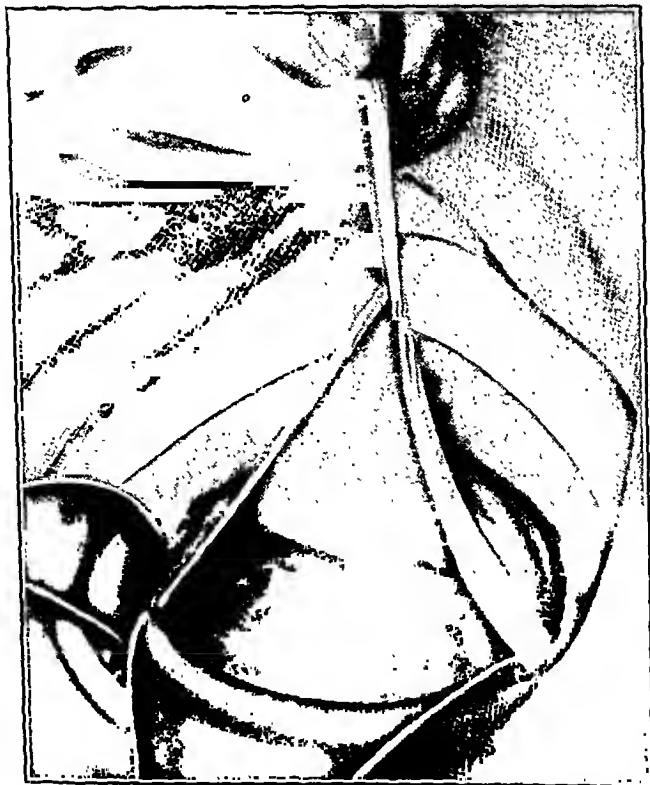


Fig. 7.—Plica completely separated, bladder retracted down with large curved retractor. (Forceps demonstrates mobility of plica.)



Of the various extraperitoneal operations, Jellinghaus' revival of interest in the Latzko technique has made it one frequently used.

The Latzko technique embodies certain features and hazards which sharply curtail its use and confine its appeal. The lateral displacement of the bladder carries the operation into an easily infected zone of restricted space, and compromises the safety of important structures.

The direct supravescical approach is by every criterion the logical one, and when combined with procedures designed to eliminate the objections to other techniques, gives an extraperitoneal operation of an ideal type.

The operation described in this paper seems to fulfill such requirements. It is truly extraperitoneal, and meets all demands for safety. Of outstanding importance is the fact that the technique is attained by operators of average ability, and it has been successfully performed by obstetric residents without special surgical training. In the entire series reported, there were no serious accidents and no maternal deaths. The accident of peritoneal puncture has been eradicated by familiarity with the technique.

It is our belief and hope that further experience in other hands will demonstrate the factors of technical facility, safety, celerity, and satisfactory results which we believe it commands.

NOTE: When this manuscript was submitted for publication, more than 60 operations of the type described had been successfully performed with two fetal and no maternal deaths. These were largely done on "bad risk" cases.

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#### DISCUSSION

DR. HENRY T. BURNS.—Before I wrote my first paper on the Latzko operation, I reviewed the literature and neither in German nor American writings was there any detailed description of how the Latzko cesarean section should be performed. All we could find was that the bladder should be displaced to the right, the peritoneal reflection upward, exposing the lower uterine segment by a longitudinal incision.

I have had difficulty in only three of the 58 Latzko operations I have performed. This occurred when the drain was removed before the drainage tract was well established. By passing a sound, opening up the tract and thus obtaining free

The operating time is of interest, recalling the objection that extraperitoneal operations are long, time-consuming operations, and conducive to surgical shock. In the author's personal group, the operating time ranged from 29 to 60 minutes. Excluding the first two cases, each one hour long, the average operating time for 17 cases was 38.5 minutes. The operating time for the entire group ranged from 29 to 82 minutes, averaging 54 minutes.

The average stay in the hospital was 18 days, although half of the patients were discharged within 14 days. One case each of bronchopneumonia, pulmonary infarct and thrombophlebitis, and antepartum and puerperal psychosis with stays of 23, 52, and 23 days affected the average stay. All patients were kept until healed and ambulatory.

Exact data were available on hours of labor and ruptured membranes in 30 cases. The average hours of ruptured membranes was  $38\frac{1}{2}$ , two-thirds of the group had ruptured membranes more than 24 hours. Labor had been present for an average of 53 hours. All but one had labored more than 24 hours, and 21 had pains more than 48 hours. Fourteen cases had fever preoperatively. Twenty-six cases had postoperative morbidity, although in 20 cases the temperature was normal after the third day even though in a few instances the drainage was purulent.

*Operative Accidents.*—In earlier experience the peritoneal cavity was opened six times before the uterus was incised, and immediately repaired. In one instance the peritoneum was noted as lacerated after extraction of a 9.25 pound baby.

Six babies weighed over 9 pounds, one over 10. One had a tremendous hydrocephalic head which well tested the operative field and uterine incision capacity. The patient had a 35-minute operation, without peritoneal laceration, after 48 hours of labor. There was a slight temperature for 6 days, and the patient was discharged in 14 days. The indication for abdominal delivery over delayed craniotomy was on religious grounds of the patient's election.

As noted in the table, cephalopelvic disproportion accounted for 27 of the operations. Of the 3 patients previously sectioned, 2 were not seen until labor with ruptured membranes had progressed for many hours beyond the "12-hour safe period." One, in spite of clinic talks and warnings, came in with a history of ten days' ruptured membranes. The third had defect in the old scar the size of a dime. The defect, obviously long existing, was clean and bloodless. Forty-eight hours of labor had not extended the defect in the lower segment of the uterus, although the membranes had ruptured through it, distending the retrovesical area with amniotic fluid!

Six patients had wound infections in and about the site of drainage, and 2 wounds were grossly infected although all eventually healed well. The remainder healed promptly after removing the supravescical drain.

#### SUMMARY

In presenting this technique, recognition is extended to previous observers and operators who attempted the same or similar approaches to the lower uterine segment. From Physick in 1824 to Furness in 1930, this approach has repeatedly seemed the most rational and direct. The difficulty largely seems to have been in not using incisions through the perivesical fascia, not freeing the bladder adequately from the uterus, not distending and emptying the bladder in the early stage of the operation, not fully utilizing the lower segment of the uterus for the incision, and not using an incision designed to facilitate the extraction of a large size baby's head.

The various transperitoneal operations developed in the search for satisfactory true extraperitoneal operations are effectual for the usual case. But one cannot expect consistently good results in presumably or actually infected cases. It is in this group that the true extraperitoneal operation affords the greatest protection to the patient and solace to the obstetric surgeon.

In doing cesarean section at the Woman's Hospital, we almost invariably use a transverse incision in the lower uterine segment.

DR. WATERS (closing).—In answer to Dr. Halsted who regards the operation as dangerous, I would say that the first five minutes may be said to be meticulous, very slightly dangerous, but not difficult. The rest of the operation is as simple as any low laparotrachelotomy. The entire procedure depends upon getting the peritoneum, with its perivesical fascia attached, off the fundus of the bladder. There is plenty of room, for I delivered one baby with a tremendous hydrocephalic head. I defy any Latzko approach, even with the excellent addition of deliberately incising the peritoneal fold, to provide room for that particular head.

After the first case, in which the operation was deliberately planned and done, I looked for suitable cases in order to develop the technique; not finding them fast enough, I did this operation on several cases where elective procedures were to be done. It was just as easy as those of the other type.

I put in a self-retaining catheter, because with that much manipulation in the pelvis it is wise to give the bladder a rest for forty-eight hours. The catheter keeps the bladder collapsed.

## THECA CELL TUMORS OF THE OVARY\*

### A REPORT OF TEN CASES

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(From the Section on Surgical Pathology, The Mayo Clinic)

IN 1932 Löffler and Priesel<sup>1</sup> described six "xanthic" tumors of the ovary which they considered as arising from the cells of the theca interna. In 1934 these same authors added four similar cases. Their reports were followed by those of Melnick and Kanter,<sup>2</sup> Kellert,<sup>3</sup> Geist and Speilman<sup>4</sup> and others. In 1938 Geist and Gaines<sup>5</sup> added a comparatively large series of 5 cases and brought to 22 the number of recorded theca cell tumors. The gynecologic literature now contains about 25 examples of this rare neoplasm.

### HISTOGENESIS

Much controversy has arisen not only as to the histogenesis but also the actual nature of these tumors. Löffler and Priesel early recognized the close resemblance between the cells of the tumor and the cells of the theca interna itself. However, most of the tumors they reported were large, so that an actual point of origin could not be definitely established. Others disagreed and at present there are three theories to explain the origin of theca cell tumors. Proponents of the first theory believe these neoplasms are derived from the ovarian stroma and regard them as luteinized fibromas. A second group holds that the tumors are luteinized granulosa cell tumors and that they should not be called "theca cell tumors." Finally, many prominent gynecologists believe with Löffler and Priesel that the tumors arise from theca cells and represent a separate entity. Experimental evidence would tend to support this third view.<sup>6</sup>

\*Submitted for publication, September 8, 1939.

drainage I have always succeeded in obtaining prompt healing of the wound and subsidence of temperature. I have never seen the ureters, though I make it a practice of looking for them. There were no maternal deaths in my 58 cases.

From the way Dr. Waters has described this technique and from the results he has obtained, I am inclined to think that this procedure carries with it much less danger than the Latzko extraperitoneal cesarean section. We should have some one in every community who can do a true extraperitoneal cesarean section of some type on frankly infected patients. In this way we can obtain a living baby instead of sacrificing the baby or the uterus through a Porro cesarean section.

DR. HARBECK HALSTED.—I see no reason why this operation should take the place of the Latzko operation in the frankly infected case. It is more difficult to do, it has no great advantages, and I think the results will prove no better.

Formerly I believed that the extraperitoneal operation should be used in all cases. I first did one on a patient who was in labor about four hours with very great ease. I then tried it on two patients who had not been in labor at all. In the first instance it was done extremely easily, but in the second case the dissection between the bladder and the uterus was very difficult, but it was eventually accomplished.

I feel with Dr. Burns that the extraperitoneal operation is an extremely valuable operation, that it is not done often enough, and I would like to see it developed, so that it can be used on patients who have not been in labor.

DR. ALFRED C. BECK.—From a long experience with the transperitoneal low cesarean section, I am satisfied that many of the neglected cases should be handled by the transperitoneal route.

This procedure does not appear to be very difficult and, because not only peritoneum but fascia and bladder separate the uterine wound from the peritoneal cavity, it should give greater protection than any of the other cesarean techniques.

The original extraperitoneal procedure was recommended by Physick who was an anatomist and not a surgeon. He recommended it to Dewee, who referred to it in a footnote in one of the early editions of his textbook. Dewee apparently did not do the operation and omitted it from subsequent editions of his book.

Early in this century, Frank and Selheim actually tried the operation as suggested by Physick. They attempted to separate the peritoneum from the paravesical fascia and enter the uterus through the space thus prepared. Because of their inability to dissect off the peritoneum, Kroenig devised his transperitoneal low section which he thought would accomplish the same purpose, since the uterine wound was covered by peritoneum and the bladder. The operation of Dr. Waters is a distinct improvement and merits a trial.

DR. ALBERT ALDRIDGE.—At the Woman's Hospital, we have adopted the extraperitoneal cesarean section for selected cases and have done about 40 such operations with only one death. This was due to late embolism at a time when the patient was free of postoperative fever.

Some time ago, I reported before this Society, on the results of a series of cases that had been operated upon at the Woman's Hospital and suggested some modifications in the Latzko technique. These modifications included a procedure to provide more room for the delivery of the child. We found that under the most favorable conditions the space that could be had by careful dissection was frequently so small that there was great risk of injury to the bladder or uterovesical fold during extraction of the child.

I had considered a modification in the technique exactly like the one which Dr. Waters has presented and had tried to carry out the same procedure by blunt dissection. The uterovesical fold is usually so adherent to the fundus of the bladder, that I am convinced these structures cannot be separated except by sharp dissection. If experience proves that we can routinely carry out the dissection as described by Dr. Waters, without too much danger of injury to the bladder or uterovesical fold of peritoneum, I feel that he has added an important step in the technique of extraperitoneal cesarean section. This seems the most logical approach to the lower uterine segment.

CASE 1.—A white multipara, 56 years old, came to the Mayo Clinic on May 23, 1938, complaining of postmenopausal bleeding. Her family history and personal history were irrelevant. Menstrual history had been normal, her three pregnancies uncomplicated, and her menopause at the age of 50 was without unusual incident. Four years prior to admission her present illness had begun with a resumption of "menstruation." These episodes of bleeding occurred with approximately cyclical regularity every two or three weeks, usually lasted three to five days, and were frequently accompanied by the passage of large clots of blood. A slight purulent "intermenstrual" discharge had been noticed for six months.

Examination disclosed an enlarged uterus with a palpable right ovarian mass which was slightly tender. Results of laboratory examinations were essentially negative.

At operation on May 28, 1938, subtotal hysterectomy was done with removal of the adnexa because of uterine fibroids and a solid tumor which involved the right ovary. The patient was dismissed twenty-three days later, following a normal convalescence.



Fig. 1.—(Case 1.) Posterior view of a theca cell tumor of the right ovary, with an enlarged uterus which contains fibromyomas.

The operative specimen consisted of the uterus, both Fallopian tubes and both ovaries. The uterus was large and contained multiple small fibromyomas. Both tubes and the left ovary were normal on gross inspection. The right ovary was enlarged and on section presented a brownish yellow, solid, tumor nodule, 3 cm. in diameter (Fig. 1).

Histologic sections of interest were limited to the endometrium and the right ovarian tumor. The latter was seen to consist of plump spindle cells with central nuclei and relatively prominent nucleoli. The nuclei were oval, dark-staining and showed on an average, three mitotic figures per thousand cells. The cytoplasm was relatively clear, finely granular, and occasionally vacuolated (Fig. 2, a). Fibrous tissue was not abundant and tended to be arranged in bands which showed partial hyalinization. Around these portions the tumor cells appeared in palisade formation. Stains for lipid revealed the presence of fat in the tumor cells, especially in relation to the zones of hyalinization (Fig. 2, b). The remnant of normal ovary which lay stretched out over the surface of the tumor showed an entire lack of maturing follicles and corpora lutea. The endometrium was polypoid and reflected in most sections the action of estrin. Here and there, however, were

## CLINICAL FEATURES

The clinical features usually associated with theca cell tumors resemble closely those found in association with granulosa cell tumors of the ovary. More than 80 per cent of the neoplasms occur after the menopause and produce vaginal bleeding which may or may not be periodic. Those tumors reported among patients of the younger age groups have usually been associated with amenorrhea or with metrorrhagia. The clinical picture is usually not so uniform as it is in the presence of a granulosa cell tumor, and some theca cell tumors apparently produce no menstrual abnormalities. As with granulosa cell neoplasms, the symptoms are caused by the secretion of estrin by the cells of the ovarian neoplasm as demonstrated by assay of tumorous tissue.

## PATHOLOGIC FEATURES

Despite arguments to the contrary, there seem to be certain gross and microscopic features peculiar to all neoplasms of this so-called theca cell group. The tumors are fibrous, solid, usually encapsulated and are canary yellow in color. On section the "liver sausage" consistency of granulosa cell tumors is lacking and, except for the yellow color, a diagnosis of fibroma would seem justified on the basis of gross inspection. A thin "rind" of ovarian tissue can usually be shelled from the surface of the tumor in the form of a smooth "capsule."

Histologically, the cardinal features are the predominance of plump fusiform cells with vacuolated cytoplasm and oval nuclei. An epithelioid appearance is sometimes assumed. Intracellular fibrils are often abundant, in contradistinction to the picture seen in specimens of granulosa cell neoplasm. The tumor cells and the interstitial substance both tend to undergo extensive hyalinization—a process which often occurs in irregular bands. Stains for lipid reveal the presence of fatty droplets within the cytoplasm of the tumor cells and, to a lesser extent, in the intercellular substance. These fatty deposits tend to be more concentrated about the periphery of the zones of hyalinization. The distribution of lipid differs from that observed in luteinized granulosa cell neoplasm, in that it is intracellular. Chemically, also, a difference exists.

## MATERIAL AND METHODS

A review of the pathologic material examined at the Mayo Clinic revealed 10 ovarian neoplasms with gross and microscopic features which warranted a revised diagnosis of theca cell tumor. Multiple sections were recut from these tumors and stained routinely with hematoxylin and eosin. In addition, stains for lipid were made in every instance as confirmatory diagnostic evidence. The pathologic and clinical features of these ten cases as herein reviewed, are submitted not with the idea of settling controversial issues concerning histogenesis, but with the purpose of adding to the literature examples of a tumor which, until recently, has received little attention in gynecologic writings.

The essential, positive observations on examination were uterine fibromyomas and mild hypertension.

At operation on May 10, 1929, hysterectomy with bilateral salpingo-oophorectomy and appendectomy were performed because of uterine fibromyomas and a solid left ovarian tumor. The patient was discharged on the nineteenth day postoperatively. Six years later she reported herself as being in excellent health.

The pathologic findings were almost identical to those described for Case 1 and will not be detailed. The theca cell tumor measured 2 cm. in diameter and involved the left ovary (Fig. 3, *a*). The uterus was enlarged (195 gm.) and contained small

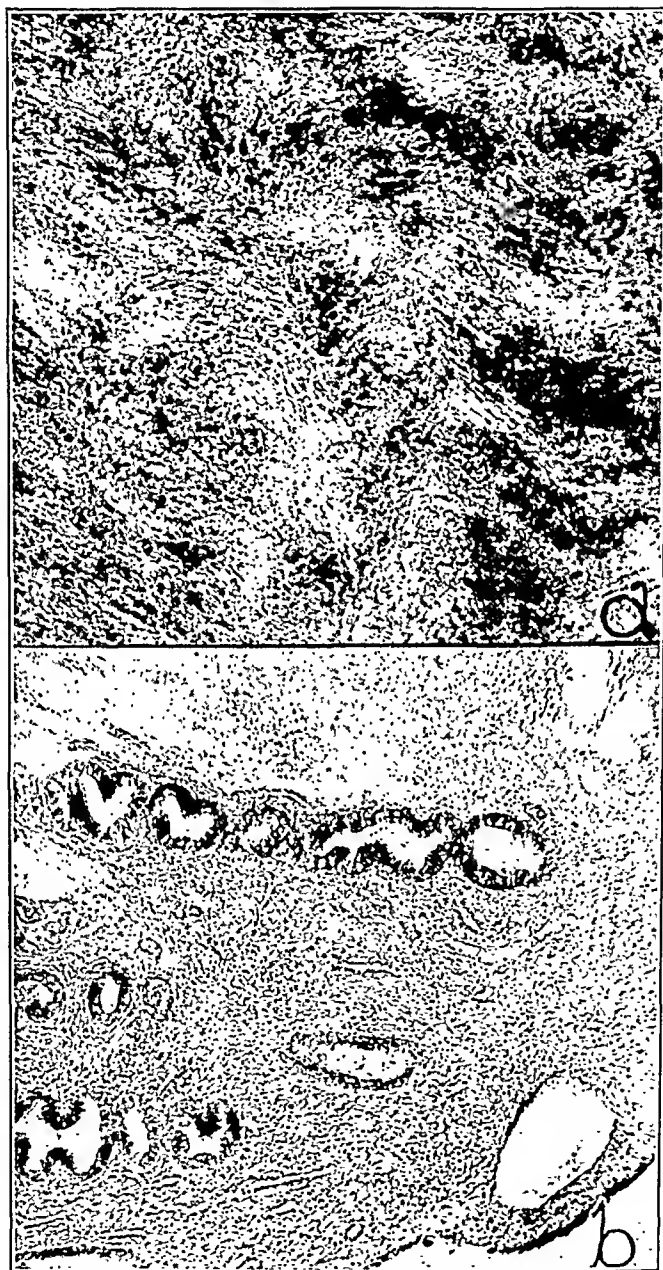


Fig. 3.—*a* (Case 2). Theca cell tumor of the left ovary, with a large amount of intracellular lipoid. Some hyalinization is present in bandlike regions (sudan III;  $\times 100$ ); *b* (Case 2), region in endometrium showing coiling of tubules; a "progesterone" effect is suggested (hematoxylin and eosin;  $\times 10$ ).

regions wherein the glandular tubules were slightly coiled so as to suggest an early secretory or differentiative phase. Cysts were fairly numerous and suggested a lack of the hormone of the corpus luteum.

CASE 2.—A white multipara, 53 years old, entered the clinic May 8, 1929, complaining of postmenopausal bleeding. The patient's history was irrelevant. Her menstrual periods had been scanty and irregular for two years, and one year prior to admission they had ceased for a period of six months. Six months prior to admission the "menses" had returned, somewhat irregular in time and duration.

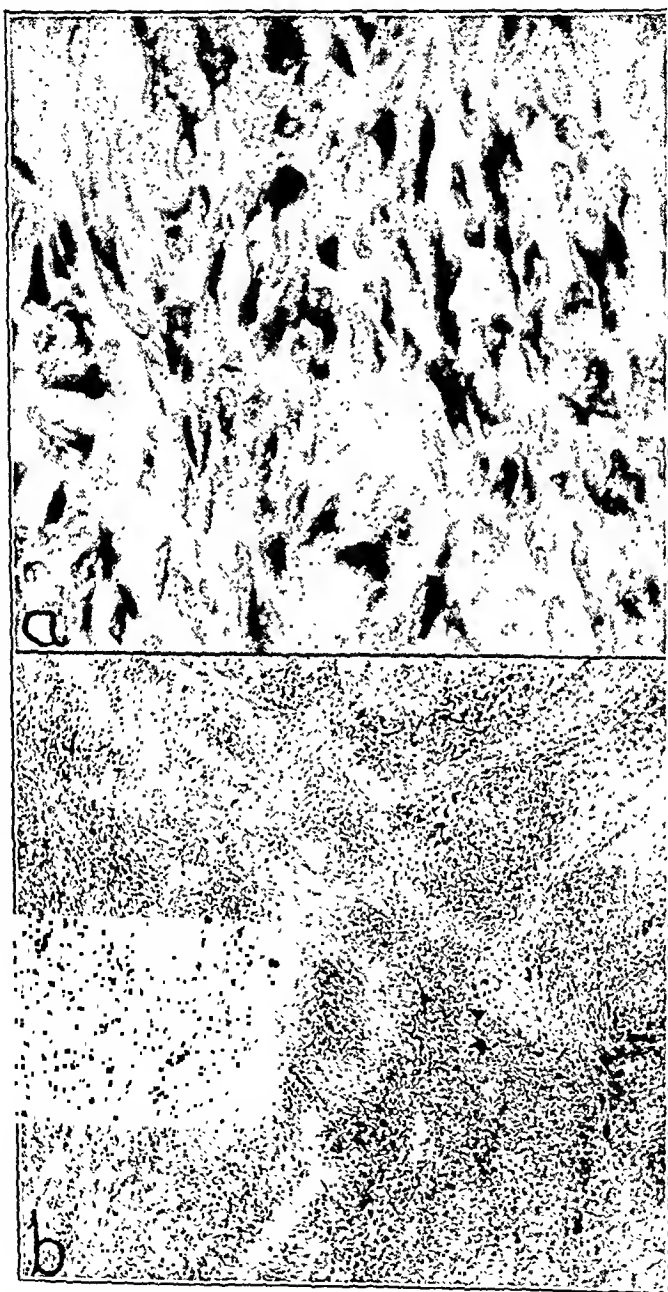


Fig. 2.—*a* (Case 1). Section of a theca cell tumor of the ovary, the cells of the tumor presenting a spindle-like appearance, but the granulosa cells being, in contrast, round (hematoxylin and eosin;  $\times 600$ ); *b*, section of a theca cell tumor (same case as Fig. 2*a*) showing deposits of lipoid concentrated around zones of hyalinization (sudan III;  $\times 100$ ).



Examination disclosed an enlarged, boggy type of uterus and a mass in the region of the left adnexa.

At operation on Jan. 20, 1914, hysterectomy with bilateral salpingo-oophorectomy was done because of a solid tumor of the left ovary. The patient was discharged on her fourteenth day postoperatively. Efforts to follow this patient proved unsuccessful. Grossly, the uterus was considerably enlarged, measuring 6 by 5 by 4 cm. (Fig. 4). The endometrium was thickened. Both Fallopian tubes presented chronic inflammatory changes. The right ovary was atrophic. In the left ovary was a yellowish, solid, encapsulated tumor nodule 3 cm. in diameter. Histologically, this tumor was seen to be composed of plump spindle cells loaded with lipid. Hyalinization was seen in handlike portions in many sections (Fig. 5). Mitoses were scanty. The endometrium was of the glandular cystic type, with little evidence of activity of the hormone of the corpus luteum.

CASE 4.—A white multipara, 55 years old, entered the clinic on Oct. 4, 1924, because of a continuous blood-tinged vaginal discharge two years in duration. Ten years previously she had passed through an apparently normal menopause.

Pertinent observations were limited to the pelvis, where a tumor was palpated in the left adnexal region.

At operation on Oct. 10, 1924, hysterectomy with bilateral salpingo-oophorectomy was performed because of a solid tumor, 6 cm. in diameter, involving the left ovary. The patient was well when she was last heard from on Dec. 6, 1931. Pathologic observations were a slight enlargement of the uterus, which structure contained cystic endometrium. The condition of both Fallopian tubes and the right ovary was not remarkable. The left ovarian tumor measured 10 cm. in diameter, was solid in consistency, and yellow in color. Histologically, it presented all the typical features of a theca cell tumor. Hyalinization was a prominent feature.

CASE 5.—A white primipara, 26 years old, entered the clinic on May 15, 1911, with the complaint of easy fatigability. Menses had begun at the age of 18 years and had always been irregular and scanty. For the preceding year mild vaginal bleeding had been a daily occurrence.

Pertinent observations on examination were a symmetrically enlarged thyroid gland, compensated mitral heart disease, an enlarged uterus, and a nodular pelvic tumor.

At laparotomy on May 24, 1911, a yellowish fibroid tumor involving the left ovary was removed and appendectomy was performed. The patient was dismissed from the hospital on the eleventh day postoperatively. She was living and well when last heard from in 1931.

The ovarian tumor measured 5 cm. in diameter, was yellow in color, and fibrous in consistency. Histologically, it proved to be a theca cell tumor with extensive deposits of lipid.

CASE 6.—A white primipara, 48 years old, entered the clinic on Jan. 3, 1910, complaining of a pelvic tumor. Her history was irrelevant to her condition at entrance. Her last menstrual period had occurred one year previously. Two years prior to admission a pelvic tumor had been discovered in the course of a medical examination for "irritable bladder."

Examination disclosed a large, firm, freely movable mass in the posterior portion of the cul-de-sac of Douglas.

At operation on March 30, 1910, subtotal abdominal hysterectomy was done, with removal of the adnexa because of a solid tumor of the right ovary. The peritoneal cavity contained a small amount of free fluid. The patient reported "no recurrence of trouble" in 1915.

The right ovarian tumor was solid and measured 4 cm. in diameter. Histologically it presented the characteristics of a theca cell tumor, but contained only a moderate amount of lipid substance. The endometrium was cystic and rather atrophic.

CASE 7.—A white multipara, 58 years old, entered the clinic on July 13, 1934, complaining of postmenopausal bleeding. Her history was irrelevant to her condition at entrance. Menses had always been regular and her menopause at the

fibroids. The endometrium was cystic and reflected the action of estrin, but certain regions contained coiled glands suggesting the influence of progesterone (Fig. 3, *b*).

CASE 3.—A white multipara, 56 years old, entered the clinic on Jan. 17, 1914, complaining of persistence of her menstrual periods. For seven years menses had been prolonged, with heavy flow. For one year she had menstruated almost daily.



Fig. 4.—(Case 3.) Theca cell tumor of the left ovary, showing grossly an extreme degree of uterine myohyperplasia and thick endometrium.



Fig. 5.—(Case 3.) Typical microscopic picture of a theca cell tumor with extensive hyalinization. The dark-staining areas represent lipid accumulation (sudan III;  $\times 100$ ).

The ovarian tumor was solid, yellowish, and measured 15 cm. in its greatest diameter. It could best be described as a "yellow fibroma." Histologically most portions of the tumor were typical of theca cell tumor with rather extensive hyalinization. In other portions, however, the picture was that of a granulosa cell tumor of the cylindroid type (Fig. 6, *a* and *b*).

CASE 8.—A white multipara, 58 years old, came to the clinic on July 9, 1931, complaining of vaginal bleeding of one month in duration. The bleeding had begun as a frank flow of bright red blood and had continued as a blood-tinged discharge. The patient's history otherwise was irrelevant to her condition.

Essential observations on examination were an adenomatous goiter and an enlarged uterus.

On July 11, 1931, dilatation and curettage revealed a carcinoma of the fundus uteri. Abdominal hysterectomy was thereupon carried out, with removal of both adnexa. On several subsequent visits there was no evidence of recurrence of malignancy. In January, 1939, the patient reported that she was well.

Pathologic features of interest were the large uterus, which weighed 200 gm. and which was the seat of a Grade 2 (on the basis of 1 to 4) adenocarcinoma measuring 3 by 3 by 2 cm. The condition of both Fallopian tubes and the right ovary was not remarkable. The left ovary was the seat of a solid neoplasm 4 cm. in diameter, which was smooth on surface and yellowish on section. Histologically, this proved to be a typical theca cell neoplasm.

Cases 9 and 10 presented incidental observations—one (Case 9) an accidental finding of a theca cell tumor 1 cm. in diameter afflicting an elderly patient dying of bronchopneumonia, and the other (Case 10) a theca cell tumor 2 mm. in diameter discovered in a patient undergoing hysterectomy for fibroid tumor. In neither instance were there any clinical symptoms suggestive of ovarian pathologic processes.

#### COMMENT

In the present study all the specimens were preserved in formalin, a circumstance which precluded hormonal studies. However, certain data are at least suggestive of a hormonal effect. Of 8 uteri available for examination, 7 were considerably enlarged and 3 contained fibroid tumors. The endometrium, also, in 6 of these 8 cases, was of the glandular cystic type, reflecting the prolonged action of estrin, probably unopposed by the action of progesterone. In two instances the endometrium presented evidence of glandular coiling indicative of differentiation and suggestive of a progesterone effect.

The one example (Case 8) of an associated endometrial carcinoma is interesting. In a series of 32 cases of granulosa cell neoplasms, we have seen 3 cases with associated carcinoma of the endometrium and other investigators have reported a similar finding. This incidence of 10 per cent seems more than coincidental and raises the question of the carcinogenetic properties of estrin.

All the neoplasms fulfilled the gross diagnostic criteria laid down for theca cell tumors and 8 of the lesions were typical histologically. In 2 instances histologic features typical of granulosa cell neoplasm were present in scattered regions throughout the tumor. This observation is not new, having been previously reported by Greenhill and Greenblatt.<sup>7</sup>

Nine of the 10 patients were more than 45 years of age. This is in keeping with the observations of others that theca cell tumors occur most frequently after the menopause. It has been generally conceded that theca cell tumors are, at most, of a low grade of malignancy.

age of 48 had had no unusual features. Her present illness had begun one year prior to admission and took the form of two episodes of vaginal bleeding associated with lower abdominal cramping pain of menstrual type. A tumor of the left ovary had been discovered on routine physical examination four years previously.

Examination disclosed a tumor in the left side of the pelvis. The possibility of this tumor's being a granulosa cell neoplasm was considered. Operation was advised but was deferred by the patient.



Fig. 6.—*a* (Case 7). Section of a typical theca cell tumor, with bandlike regions of hyalinization (sudan III;  $\times 100$ ); *b* (Case 7), another region of the same tumor; some of the cells are definitely of the granulosa type (hematoxylin and eosin;  $\times 100$ ).

She returned two years later because the abdominal tumor seemed to be increasing in size. Examination confirmed this suspicion and on April 14, 1936, exploration was carried out. Left salpingo-oophorectomy was done because of a large solid tumor which involved the left ovary. Postoperative convalescence was normal and the patient was dismissed after nineteen days of hospitalization.

*Race.*—Ninety-three (or 79.5 per cent) of the patients were white, and 24 were negroes.

*Age.*—One hundred eight surviving patients were distributed according to age (Table I). In the following column these figures were transposed into percentage distribution. In the last column is given for control a similar distribution found by Jensen (p. 157).

*Gravidity.*—One hundred eight surviving patients were similarly distributed according to parity (Table II).

TABLE I

AGE GROUP	NO.	PERCENTAGE DISTRIBUTION	CONTROL
19	18	17	4
20-24	33	30	24
25-29	28	26	29
30-34	15	14	23
35-39	9	8	14
40-	5	5	6
Total	108	100	100

TABLE II

PARITY	NO.	PERCENTAGE DISTRIBUTION	CONTROL*
0	44	41	38
1	31	29	20
2-4	24	22	28
5 plus	9	8	14
Total	108	100	100

\*Jensen, J.: *The Heart in Pregnancy*, St. Louis, 1938, The C. V. Mosby Co., p. 194.

TABLE III

Rheumatic heart disease	99
Congenital heart disease	7
Syphilitic heart disease	2
	108

*Etiology.*—Etiologically the patients were distributed as shown in Table III.

Thus, 89 per cent of these patients had rheumatic heart disease. That 7 patients had congenital heart disease is almost three times as many as expected (Jensen, p. 296). We were very critical in the diagnosis of congenital heart disease and are well aware that functional murmurs may closely mimic congenital heart disease. Nevertheless, we believe the diagnosis is beyond doubt in these 7 cases, though we failed to diagnose the exact lesion in 3. In 3 others, patent ductus arteriosus and in one Roger's disease was thought to be the dominant lesion. None of the patients were markedly cyanotic. Both of the patients with syphilitic heart disease had aortic regurgitation and positive serologic tests for syphilis.

Patients who had hypertension or other evidence of degenerative heart disease and who did not at the same time suffer from any other form of organic heart disease were not included in the series. Reference to two patients with kyphoscoliotic heart disease has previously been published (Jensen, p. 337).

*Anatomic Lesion.*—Ninety-nine surviving patients with rheumatic heart disease presented valvular lesions as shown in Table IV.

Six foot films of the chest were taken of 64 patients. In 13 cases the cardiac shadow was within normal size, but in only 7 also of normal shape. In 42 cases the left border showed the convexity characteristic of mitral disease. Twenty-two cardiac shadows were enlarged 1 degree, 14 were enlarged 2 degrees, and 6 were enlarged 3 degrees.

The present series does not argue much for or against this point. All that can be said is that, on the basis of traced patients, the prognosis following removal of theca cell tumors is much better than it is for solid carcinomas of the ovary.

#### SUMMARY

The clinical and pathologic data on 10 so-called theca cell tumors have been presented. These tumors occur most frequently following the menopause. They resemble granulosa cell tumors clinically, but pathologically possess certain distinguishing features which probably justify their consideration as an entity.

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## HEART DISEASE AND PREGNANCY

### AN EIGHT YEARS' EXPERIENCE

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#### INTRODUCTION

ON NOV. 1, 1930, the Medical Consulting Service of the Prenatal Clinic in the Department of Obstetrics of Washington University was reorganized. One afternoon a week a member of the Obstetrical Staff (C. W.) and one internist (J. J.) examine together all obstetric patients who present medical problems, a great many of which are referable to the cardiovascular system. Those found to be suffering from organic heart disease receive special records which are kept in a separate file. From Nov. 1, 1930, to Dec. 31, 1938, the clinic has followed 108 such patients. Five additional patients were included in this study, because they presented points of special interest; they were all seen in St. Louis Maternity Hospital. The subsequent analysis is made to determine to what extent the care extended to this class of patient has affected maternal and infant death rates.

#### ANALYSIS OF MATERIAL

*Incidence.*—The experience of Washington University Obstetrical Department regarding incidence of heart disease conforms quite well to the general experience on these points. During the period of observation 8,843 patients were registered in the Clinic. One hundred and twelve, or 1.27 per cent, of these were found to have heart disease.

However, our experience may not reflect the true incidence of the defect, for because of the relatively small value of the electrocardiogram in this problem, only 27 of our cardiac patients were electrocardiographed.

*Interruption of Pregnancy.*—Thirteen, or 11.4 per cent, of all pregnancies observed ended with the death of the baby. One patient had a spontaneous miscarriage, two babies died undelivered, and three pregnancies were interrupted before the child was viable. Three were stillborn and 4 died post partum. However, if only those cases were considered in which the pregnancy was carried beyond thirty-six weeks, the death rate was only 4, or 3.79 per cent.

Artificial interruption of pregnancy was performed only twice, and we do not believe that so conservative a management did any substantial harm to the mothers. Thus our experience confirms the view prevailing in the literature that premature interruption of pregnancy should be restricted to those cases where congestive failure fails to respond to the best available treatment.

*Maternal Deaths.*—During the period under consideration, 8 women died in St. Louis Maternity Hospital with heart disease. Their cases are here briefly abstracted.

CASE 1.—(No. 13450.) Primigravida, aged 40 years. History of rheumatism in childhood. Rheumatic, mitral heart disease. Blood pressure: 190/140. Admitted when thirty-two weeks pregnant with congestive failure which progressed in spite of medical treatment. After nine days in hospital, Cesarean section. Child lived. Anesthesia: pantopone, hyoscine, local. Two hours after operation collapse and death. No autopsy.

CASE 2.—(No. 14106.) Colored primigravida, aged 18 years. When four months pregnant, she developed dyspnea. Pneumonia and colds during next three months. When seven months pregnant she appeared at St. Louis Maternity Hospital. As she was not very sick she was told to return next day. She arrived by street car at 2 P.M. She had dyspnea which rapidly increased, and she developed pulmonary edema from which she died at 9 P.M. Post-mortem examination: button hole mitral stenosis. Heart's weight 235 Gm. Pulmonary edema.

CASE 3.—(No. 14677.) Tertigravida. Two previous miscarriages. Double mitral lesion. When twenty-eight weeks pregnant, she developed an upper respiratory infection. Against instructions she stayed away from the Clinic. Near term she was admitted to the St. Louis Maternity Hospital in labor. When the os was fully dilated she suddenly became cyanotic and dyspneic. She was rapidly delivered of a living infant. Following this she continued to improve for about twenty-four hours when she relapsed and died with pulmonary edema, about thirty-eight hours post partum. Post-mortem examination: the heart weighed 865 Gm. Marked mitral stenosis. Pulmonary edema. Congestion of liver. No peripheral edema.

CASE 4.—(No. 15943.) Quadrigravida, aged 26 years. Mitral stenosis. Rheumatic fever aged 7. Decompensated (?) during last two pregnancies at six and eight weeks, respectively. Entered Maternity Hospital on Jan. 4, 1933, twelve weeks pregnant, because of cardiac symptoms. On Jan. 14, 1933, hysterectomy. Morphine, hyoscine, local anesthesia. Four days postoperatively she developed right lower lobar pneumonia. Sixteen days postoperatively collapse and death. No autopsy.

CASE 5.—(No. 20699.) This case of subacute bacterial endocarditis has been reported in detail by Jensen (p. 288).

CASE 6.—(No. 21531.) Decigravida, aged 38 years. Eight pregnancies ended in miscarriages, 6 of which were induced. One living child was born at seven months. Chorea at 14, rheumatic fever at 16 years of age. First seen at the St. Louis County Hospital, when four months pregnant, with mitral stenosis and regular rhythm. Early decompensation. She was admitted to St. Louis Maternity Hospital and responded well to treatment. During the next two or three months, she was followed as an out-patient at the County Hospital. At seven months, when hardly compensated she was delivered of a seven months' baby which died soon

TABLE IV

	NO.	PERCENTAGE DISTRIBUTION	CONTROL JENSEN (P. 170)
"Mitral"	3	3	--
Mitral regurgitation	11	11	40
Mitral stenosis	35	35	20
Mitral stenosis and regurgitation	39	40	29
Aortic lesions	4	4	4
Aortic and mitral	7	7	5
Total	99	100	98

TABLE V

CLASS	NO.	PERCENTAGE DISTRIBUTION	CONTROL (JENSEN P. 41)
I	46	39	36
II, a	44	37	32
II, b	25	21	24
III	4	3	8
	119	100	100

*Cardiac Function.*—Arrangement according to the functional classification of the American Heart Association is shown in Table V. All cases were here included.

Twenty-seven (or 22.7 per cent of all the cases) patients showed, some time during the pregnancy, signs of congestive failure (i.e., rales, edema, dyspnea, and tachycardia).

An attempt was made to correlate the size of the heart on the x-ray film with functional classification, but this was not feasible, possibly because the number of cases was too small.

*Acute Rheumatic Carditis.*—One patient had acute rheumatic carditis with symptoms so marked that the pregnancy was interrupted and the patient sterilized. The patient was followed for over four months, her course was unsatisfactory though she did not develop severe congestive failure.

*Toxemia of Pregnancy.*—Four patients with increased blood pressure were observed; in none of them did the condition progress so far as to cause serious trouble. There was no evidence that patients with rheumatic heart disease are especially liable to eclampsia. Nephritis was not diagnosed in this series.

There was nothing to show that these patients as a group did worse than a similar group of nonpregnant cardiac patients might have been expected to do.

*Abnormalities of Impulse Formation and Conduction.*—*Paroxysmal tachycardia* was diagnosed 3 times in this series. In none of them did the pregnancy seem to affect the tendency to the attacks.

*Auricular fibrillation* was found in two patients with rheumatic heart disease, both of whom died. One was the fatal Case 1 which was first seen near term, and the other was the fatal Case 6. This patient developed the arrhythmia in the final stages of her illness, at first in attacks and, later, permanently. Thus we can confirm the impression (Jensen p. 179) that auricular fibrillation is rare in pregnant women with rheumatic heart disease and that it is a sign of grave prognosis.

*Bundle branch block* was present in our fatal Case 1 and also in a 34-year-old gravida iv who had undergone thyroidectomy fourteen years before. In 1931 and in 1933 she had been delivered in St. Louis Maternity Hospital. Immediately following delivery she developed pulmonary edema and became dyspneic and cyanotic. She improved promptly under treatment and was discharged in good health. She has remained well since. Following this episode careful examination revealed signs of mitral stenosis, and x-ray examination showed marked enlargement of the heart shadow. The electrocardiogram showed bundle branch block.



TABLE VI

Sepsis	10
Toxemia	8
Obstetric complications (including hemorrhage)	9
Embolism	2
Acute infections (including pneumonia)	5
Heart disease	6
Other causes	4
	44

## TREATMENT

The group of patients observed through clinic and hospital were managed in accordance with the principles now generally accepted, and discussed in detail by Jensen (*loc. cit.* Chapter 43). Obstetric patients were referred for medical-obstetrical consultation at the slightest suggestion of cardiac pathology. If heart disease was proved, considered probable or even possible, the patients were seen at regular intervals. Proved, but compensated, cardiac patients were seen every four weeks at first, then every three or two weeks and near term at weekly intervals. If, at any time, decompensation threatened, they were, because of shortage of beds at the Maternity Hospital, at first instructed to rest at home, but if such treatment was not promptly efficacious, they were admitted to the hospital until compensation was restored.

Unless decompensation threatened, patients were not admitted to hospital until onset of labor. The management of labor itself has changed somewhat at St. Louis Maternity Hospital during recent years and this change has also affected cardiac patients.

Cardiac patients are rarely given hyoscine. This drug quite uniformly causes a definite increase in heart rate which while it has no apparent ill effect on the normal patient might be objectionable in the cardiac. Barbiturates are used in a higher percentage of the cases than in the normal group, in many instances the barbiturate is being substituted directly for hyoscine in a morphine-barbiturate combination which is quite satisfactory when properly timed.

Local anesthesia fills an important place in selected cases for actual delivery. Infiltration with 1 or  $\frac{1}{2}$  per cent novocaine of either perineum or abdominal wall, depending on the route chosen, may fill the entire anesthetic need. In some of our cesarean sections on cardiac patients at the St. Louis Maternity Hospital, we have used nitrous oxide-oxygen inhalation, keeping well within a safe oxygen margin. In other cases a combination of local and inhalation anesthesia has been used, the inhalation being employed to supplement the local during the most painful part of the procedure (usually the actual extraction of the fetus results in sufficient discomfort to the patient to make from three to ten minutes of general anesthesia desirable). If this reaction on the part of the patient can be anticipated and the supplementary inhalation begun before any painful traction is made, the delivery can usually be accomplished quickly and without undue excitation of the mother.

A definite attempt is made to eliminate as much of the second stage of labor as possible in cardiac patients. This is done by the use of forceps applied as soon as the cervix is completely dilated and the head well down in the pelvis. Such a procedure spares the cardiac mother most of the dangerous stress and strain usually attending the forceful expulsive second stage efforts.

## SUMMARY AND CONCLUSIONS

The experience from 1930 to 1938 of the Department of Obstetrics of Washington University with cardiac patients is analyzed. Patients with hypertensive or degenerative heart disease were excluded unless they also suffered from valvular disease of the heart. This material conforms fairly well with the general experience of the literature

after birth. About this time she developed auricular fibrillation. She was discharged apparently compensated. She was found dead in bed twenty days post partum. No post-mortem examination.

CASE 7.—(No. 30376.) Secundigravida, aged 32 years. Five years ago "leakage of the heart" was diagnosed. During this pregnancy, dyspnea was present, and near term she had some edema of the ankles. Near term she caught a cold. During labor she received no inhalation anesthesia. Following delivery the cold became worse and in four or five days, she developed pneumonia. Nineteen days postpartum the temperature became normal, but one week later she again developed fever associated with findings in her lungs. Diagnosis of mitral stenosis was confirmed. She died thirty-six days post partum. The child lived. No post-mortem examination.

CASE 8.—(No. 31862.) Primigravida, aged 28 years. Seen in St. Louis City Hospital, when twelve weeks pregnant, with pneumonia, syphilis, and disease of the mitral and aortic valves. At age of 18 she had had a rheumatic (?) infection. Her heart disease was considered rheumatic in nature. When thirty-eight weeks pregnant, she became decompensated, and was admitted to the hospital. At term she was delivered of a live child, but following this she continued in congestive failure which did not respond to treatment. She died at home, 7 weeks post partum.

Among the 7 patients whom we know to have died from congestive heart failure, 2 had been classified as Group 3, 3 as Class 2b, 1 as Class 2a, and 1 as Class 1. Both of these last two, however, had a third degree enlargement of the x-ray shadow of the heart. This classification was found to be a valuable, though not absolute, prognostic guide.

*The Immediate Cause of Death.*—In one the immediate cause of death was sudden pulmonary edema in the seventh month of pregnancy; in 3 it was caused by pneumonia following delivery. One died suddenly twenty days post partum, probably from embolism (she had auricular fibrillation). One died from congestive failure six weeks post partum, and one from subacute bacterial endocarditis. However, the fatal cases do not reflect the experience of the prenatal clinic:

Case 1 was a private patient admitted to the hospital when almost at term. Case 2 was first seen by us the evening when she developed terminal pulmonary edema. Case 5 attended the St. Louis County Hospital, and was admitted to St. Louis Maternity Hospital for study only. She never attended the regular prenatal clinic. Case 6 was first seen by us when she was in the hospital with subacute bacterial endocarditis. Case 7 was a private patient and was not seen until she had developed pneumonia after delivery. Case 8 was first seen in St. Louis City Hospital and was referred to the Washington University Prenatal Clinic because of the great difficulties she presented.

Of these 8 fatal cases only Cases 3 and 4 belong to the regular series here under consideration, and of these Case 3 absented herself from the clinic during the crucial last trimester, against our expressed instructions. Case 4 was seen in the regular heart service several months before she became pregnant. She was there advised against conception, and given the proper instructions. These she neglected to carry out and as soon as her condition became known to the obstetric service (at twelve weeks), she was admitted to the Maternity Hospital. She responded so poorly to treatment that interruption was deemed imperative. She died from complications following the operation.

Thus it appears that among the regular patients with organic heart disease who followed our instructions and received adequate prenatal care from the beginning of pregnancy, there were no deaths.

Heart disease has been an important cause of death in St. Louis Maternity Hospital. Of 44 maternal deaths, 6 could directly be traced to valvular disease of the heart or its immediate complications. (Cases 6 and 8 died, not in the hospital, but still within six months of delivery, the period during which death may arbitrarily be considered to be connected with childbearing.) That is 13.6 per cent, somewhat higher than the average but in line with the experience of the Charity Hospital in New Orleans and the Boston Lying-in Hospital (Jensen p. 133). The 44 cases have been classified so as to compare with Jensen's Table XXVII.

In 1933 Kemp reported a series of patients treated with adrenal cortex with excellent results, and in 1934 he added another group. Freeman, Melick and McClusky reported a series of 78 cases with only two failures in 1936. In spite of these favorable reports, this form of therapy has had no wide distribution in this country.

Since these reports were issued, the product has been refined and concentrated, and is now available in 5 min. capsules equivalent to  $1\frac{1}{2}$  rat unit determined by the Grollman method, and in vials for subcutaneous and intramuscular injection in which each cubic centimeter is equivalent to  $2\frac{1}{2}$  rat units.\*

#### METHOD

The therapeutic dose has been based on the severity of the symptoms. For the ordinary mild nausea of pregnancy, we have prescribed one 5 min. capsule three times daily, fifteen minutes before meals. For the more severe types, the capsules have been combined with daily injections of 1 c.c. of the liquid subcutaneously. Some of the previous authors have used the injections three times a day, but we feel that this method is unsuited to routine office practice, and is therefore impractical unless the patient is hospitalized.

The degree of nausea has been recorded as follows: + nausea only and/or occasional vomiting; ++ nausea, and vomiting three or four times a day; +++ vomiting of all ingested foods; and ++++ true hyperemesis, with regurgitated output greater than the intake.

We have used this type of therapy in 50 cases. The results are tabulated in Table I.

TABLE I. SUMMARY OF EFFECTS OF TREATMENT

DEGREE	IMPROVED		UNIMPROVED	
	CAPS. ALONE	CAPS. AND INJECTIONS	CAPS. ALONE	CAPS. AND INJECTIONS
+	13	4	3	
++	6	13		2
+++	2	4		2
++++		1		

#### RESULTS

In the first group, there were 20 patients, ranging in age from 19 to 38, with 12 primiparas and 8 multiparas.

It will be noted there were three failures using the capsules alone, and none using the combined therapy. It is possible that if these three patients had received injections, they would have been benefited. However, some patients refuse injections for the ordinary mild nausea, both because of the added expense and because of fear of injections. We had no such difficulty with the more severe cases.

In the second group there were 21 patients ranging in age from 22 to 36, with 9 primiparas and 12 multiparas. In this group there were two failures. Both of these patients received the combined therapy. One of these patients was influenced by strong psychic factors (Case 5), while the other patient had a history of severe hyperemesis at the preceding pregnancy. This patient stated that she was much benefited by the injections, and although she continued to be nauseated for about five months, the nausea was much less severe than with the preceding pregnancy.

In Group 3 there were 8 cases with two failures. The first patient (Case 4) received both capsules and daily injections for two weeks. A tentative diagnosis of chronic cholecystitis was made and this was later verified by x-ray. Following delivery, this patient has continued to have recurrent attacks of nausea and vomiting. The second patient also received capsules and injections daily for two weeks without

\*These preparations have been supplied by the Difco Laboratories.

when distributed according to age, gravidity, etiology of heart disease, anatomic lesions, and cardiac function. Of the patients admitted during this period to St. Louis Maternity Hospital, 8 died within six months of delivery from cardiac causes. Only two of these had been regular patients of the prenatal clinic, and on further analysis it was found that among the patients properly handled and cooperating with the clinic, there were no deaths. This experience leaves us convinced that while some cardiac patients should not become pregnant and should have their pregnancies interrupted if they do, the large majority of them can be carried successfully to term if given adequate prenatal care.

In St. Louis Maternity Hospital heart disease takes a place among the causes of death comparable to that which it takes in Boston Lying-in Hospital and the Charity Hospital in New Orleans.

Auricular fibrillation was rarely seen, but here as elsewhere, it was found to be a serious complication. The functional classification of the cases was similar to the general experience of the literature and its prognostic value was well borne out. However, this analysis failed to establish a correlation between cardiac enlargement as shown by x-ray records and cardiac function. In one case active rheumatic carditis prevented continuation of pregnancy. There was no evidence that patients with rheumatic heart disease are especially liable to eclampsia.

The treatment of these cases has been conducted along generally accepted lines, as far as we can see, with gratifying results.

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## ADRENAL CORTEX IN THE TREATMENT OF NAUSEA AND VOMITING IN PREGNANCY

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THE use of adrenal cortex in the nausea and vomiting of pregnancy was suggested by Kemp in 1932. Kemp advanced the theory that there was a corticoadrenal deficiency in certain cases in the first trimester of pregnancy due to the failure of the adrenals to hypertrophy rapidly enough to compensate for the increased cortical demand. He based his theory on the following observations: (1) The maternal adrenal cortex undergoes hypertrophy during pregnancy. (2) First signs of corticoadrenal insufficiency in adrenalectomized animals are nausea and vomiting. (3) In Addison's disease, the earliest signs are anorexia and morning sickness, regardless of sex, and (4) post-mortem findings in hyperemesis, adrenalectomized animals, and Addison's disease are identical.

discontinued. On her eighth day in the hospital, she had a slight spell of nausea and vomiting which was immediately cleared by an injection of adrenal cortex. She was discharged on the tenth day and has had no recurrence.

On the other hand, in many cases there are undoubtedly organic factors that are not benefited by this particular therapy. In others there may be psychic factors beyond our control. And in others, even though no organic or psychic pathology is found, the treatment seems to have little effect. A few of these cases are illustrated.

CASE 4.—Mrs. K., para i, gravida ii, last normal period October 25, was first seen on December 12. Nausea was +++. She received adrenal cortex by mouth for one month and received 15 daily injections of adrenal cortex. There was no improvement. The nausea and vomiting persisted to a greater or less degree throughout the entire pregnancy, but disappeared following delivery. An x-ray of the gall bladder showed poor function. We feel that this is a chronic cholecystitis aggravated by pregnancy.

CASE 5.—Mrs. M. L., para 0, gravida ii, last normal period Nov. 18, 1938, was first seen in my office on Feb. 20, 1939. This patient had a premature baby which died shortly after birth at her first pregnancy. During her second pregnancy, she continued to vomit in spite of treatment until she was assured that the baby was viable. The vomiting immediately cleared up and there has been no recurrence.

Because of the variety of factors concerned, we feel that the only criteria of therapeutic value is the impression of the clinician. It is our impression that adrenal cortex in the treatment of the nausea and vomiting of pregnancy is a distinct advance. The response to this form of treatment is usually prompt and often spectacular. Further study of larger numbers of cases should produce more conclusive data.

#### CONCLUSION

We feel that our results, using adrenal cortex by mouth and injection, are better than with any of the previous forms of treatment, including sedatives, antispasmodics, and other endocrine preparations. Treatment of severe vomiting with acidosis should still include measures for relieving these conditions, and sedation is still a valuable adjuvant to the treatment. However, adrenal cortex by mouth and by injection seems to be curative therapy in many cases.

#### SUMMARY

1. Fifty cases of nausea and vomiting of pregnancy treated by adrenal cortex orally and subcutaneously have been reported.

2. Though the therapeutic effect is difficult to evaluate, we feel that most of the patients were markedly benefited by this form of treatment.

#### REFERENCES

- (1) Kemp, W. N.: *Endocrinology* 16: 434, 1932. (2) Kemp, W. N.: *Canad. M. A. J.* 28: 389, 1933. (3) Kemp, W. N.: *Med. Rec.* 140: 240, 1934. (4) Freeman, Wm., and Melick, Joel M.: *AM. J. OBST. & GYNEC.* 29: 602, 1935. (5) Freeman, Wm., Melick, Joel M., and McClusky, D. K.: *Ibid.* 33: 618, 1937.

improvement. No organic pathology could be found to account for the symptoms, and they cleared up spontaneously at about the fifth month.

We have had only one case of true hyperemesis, since we have been using this form of therapy, and this case was referred to us. The patient was hospitalized and responded promptly to three injections of adrenal cortex. This patient (Case 3) was the only one in the series who received any additional form of therapy. She received the usual routine of sedation and intravenous fluids and glucose.

We feel that the decrease in the incidence of hyperemesis in our own cases has probably been due to the prompt treatment of the earlier stages with adrenal cortex.

The difficulty of evaluating any method of therapy in nausea and vomiting of pregnancy is readily apparent. Most cases of nausea and vomiting will clear up during the first trimester under any form of treatment, so that the fact to be determined is whether the recovery is more rapid than with other types of treatment. Another indeterminate factor is the psychic effect of capsules by mouth and hypodermic injections on a condition which has so large a psychic factor in it. To establish a basis for comparison we have tabulated the time elapsing from the last period to the end of nausea, and from the beginning of treatment to complete relief in Table II.

TABLE II. TIME ELAPSED UNTIL COMPLETE CESSATION OF SYMPTOMS

DEGREE	AFTER LAST PERIOD	AFTER BEGINNING TREATMENT
+	64 days	8.1 days
++	83 days	13.7 days
+++	92 days	17.5 days
++++	—	—

In the patients who responded to therapy, the results were often amazing. Many patients reported immediate improvement after taking three or four capsules. Those whom the capsules did not benefit were usually relieved by two or three injections. Most of these reported marked improvement after the first injection, and complete disappearance of symptoms after the third or fourth. Several patients stopped the capsules after the disappearance of symptoms, but were forced to return to them following a recurrence of nausea. The following case reports illustrate some of the results obtained.

CASE 1.—Mrs. M. S., gravida i, para 0, last normal period Dec. 5, 1938, was first seen on March 24, 1939. Nausea was ++. She received capsules on March 24 and one injection on March 25. Four hours after the injection the patient experienced complete relief from all symptoms and there have been no recurrences.

CASE 2.—Mrs. I. S., gravida ii, para i, last normal period March 6, 1939, was first seen on April 20, 1939. Nausea was ++. She received capsules three times a day for one week and daily injections for six days. She reported some improvement after the first injection, and the nausea was completely cleared up in one week.

CASE 3.—Mrs. H. M., para 0, gravida ii, last normal period March 6, 1939, was admitted to Sibley Hospital for hyperemesis gravidarum May 18. This patient was vomiting continuously whether food was ingested or not. She was markedly dehydrated. Acetone and diacetic acid were present in the urine. She was seen by us in consultation on May 19. The usual treatment for dehydration and acidosis was instituted and the patient was given 1 ampoule of adrenal cortex twice a day. After the third injection she stopped vomiting completely and the adrenal cortex was

the ureterovesical junction. On Feb. 20, 1937, a catheter with wax tip bulb was passed through this ureter without difficulty and without showing any scratches.

On May 1, 1937, the patient reported that her last period was Feb. 10, 1937. There was a slight vaginal bleeding for some time, but this had ceased. A Gilfillen skin test indicated pregnancy. No Friedman test was made. Fifteen days later she complained of lower abdominal pain with a small amount of vaginal bleeding. Our findings were: Uterus approximately size of six weeks' pregnancy, cervix not dilated, small amount of uterine bleeding. She refused all treatment, stating that she preferred miscarriage to the possibility of an abnormal fetus. On June 5, 1937, she returned, complaining of the same symptoms (vaginal bleeding, staining, and lower abdominal pain). Examination showed: Uterus developing normally and the size of a three months' gestation, and a mass in the cul-de-sac which was soft and doughy in consistency. We advised operation because of our diagnosis of extra-uterine tumor complicating pregnancy.

On June 8, 1937, laparotomy was done and disclosed cysts of both ovaries, which appeared to be dermoids. Bilateral salpingo-oophorectomy and appendectomy were performed. Both cysts were posterior and filled the cul-de-sac. The undisturbed enlarged (two and one-half months) uterus contained an apparently normal intrauterine pregnancy. The dermoid cyst of the right ovary was three and one-half inches in diameter and nonadherent; the left was two inches in diameter and adherent to the left pelvic wall and cul-de-sac. The appendix had dense adhesions to the posterior surface of the cecum. The pathologic report read: (1) Dermoid cysts of both ovaries, (2) slight fibrosis of both oviducts, (3) normal appendix.

The patient's convalescence was uneventful and she was discharged on the twelfth postoperative day. The only endocrine therapy given was prolutin (progesterone), 1 international unit intramuscularly on June 8, 9, 11, 13, 15, 17, 19, and 21, 1937. Postoperatively the patient showed no disposition to vaginal bleeding or of the former uterine discomfort. Her prenatal course henceforth until delivery on Dec. 5, 1937, one hundred and eighty days after operation, was entirely normal. She was delivered spontaneously after a rapid and precipitous labor (first stage three hours; second stage twenty minutes; third stage four minutes). There was no abnormal bleeding or disposition of the uterus to relax. Lactation was established normally on the third day and the patient left the hospital on the tenth day, following a nonmorbid puerperium. Her breasts had dried spontaneously on the fifth day postpartum.

The routine six weeks' discharge examination on Jan. 21, 1938, revealed a perfectly normal pelvis except absence of adnexa. The patient reported that she had had one day of bleeding since leaving the hospital, and this had subsequently been followed by amenorrhea.

In contrast to the four cases reported by Notes,<sup>1</sup> we were able to find 43 cases, including his own, of this obstetric complication, reported in the literature available to us. A series of 19 cases from the literature before 1911 was reported by Manton. Manton did not specifically list these cases by author and publication. We are, therefore, unable to determine how many of his series are contained in ours.

Table I states the author and the number of bilateral dermoid cysts complicating pregnancy reported in each instance. It presents sufficient cases to show that bilateral ovarian dermoids complicating pregnancy are not as rare as the authors had thought after reading recent reports of such cases. In spite of its rarity this complication of pregnancy is of great consequence.

A consideration of the best treatment of this complication of pregnancy as gleaned from this series presented endocrinologic and surgical problems of management. Let us first consider the surgical aspect. The series of bilateral dermoids was not sufficiently large to warrant

## BILATERAL OVARIAN DERMoids COMPLICATING PREGNANCY TREATED BY BILATERAL OOPHORECTOMY

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THE purpose of this paper is to report upon a rare and interesting obstetric complication, namely, bilateral ovarian dermoids complicating pregnancy, in which bilateral ovariectomy was performed at three months' gestation, and the patient was delivered spontaneously at term. According to the available literature, 43 cases of bilateral dermoids complicating pregnancy have been reported, of which 12 were noted in the first three months of gestation. We also present a summary of the treatment used in these reported cases and the best method of management for the particular period of gestation, including a discussion of the endocrinologic and surgical aspects.

Our interest was first aroused in the subject by a personally observed case. Its rarity was suspected, but our investigation of available literature on the subject was stimulated by the timely appearance of a similar case report of Bernard Notes,<sup>1</sup> in which he states that his review of the literature revealed only three other cases.

### CASE REPORT

Mrs. A. H. W., aged 33 years, first consulted us on Oct. 26, 1936, stating she was anxious for a child by her second marriage. She had one child by her first marriage, had been widowed twelve years, and had been remarried one year. Family history was irrelevant. On Jan. 11, 1935, she had a pelvic examination which was negative; on June 5, 1935, a cyst was noted upon the right ovary. An acute pyelitis attack with pus in the urine, fever, and a white blood count of 13,000 responded to hospitalization. X-ray of the left kidney revealed a shadow in the left ureter which might be a stone. On Oct. 28, 1935, symptoms characteristic of the passage of a calculus from the left kidney to the bladder were noted, without blood and with little pus in the urine. On Oct. 17, 1936, because of severe pain in the lower left quadrant of abdomen and vomiting for about seven hours, the patient was examined at the Baltimore General Hospital, with the following observations recorded: tenderness without rigidity in the left lower abdominal quadrant; a bilateral tuboovarian mass, larger on the left, tender on the left only; white blood count 8,000 with 78 per cent polymorphonuclears; urinalysis negative. A diagnosis was made of chronic bilateral tuboovarian abscess, with an acute flare-up on the left side. Recommendations were, urogram and cystoscopy to be followed, if negative, by laparotomy.

Our findings nine days later, Oct. 26, 1936, were: an irregular, tender, doughy mass of the left adnexa, about 5 cm. in diameter, and a small cystic mass in the right adnexa. At that time a tentative diagnosis of left salpingitis, right ovarian cyst, and possible ectopic pregnancy was made. A Friedman test was negative. Six Elliott treatments gave slight relief and the left mass decreased in size.

Urogram made at the Norfolk Naval Hospital, Jan. 27, 1937, showed a triangular shaped shadow of calcium density in the lower left ureter about two inches above



TABLE II

AUTHOR	PERIOD OF GESTATION AT WHICH OPERATION WAS PERFORMED	OUTCOME OF PREGNANCY
1. Bantock <sup>35</sup>	Bilateral ovariectomy; period of gestation, third month	Delivered at full term
2. Dsirne <sup>60</sup>	Reports five cases bilateral ovariectomy but time of operation in each is not given	All delivered at term
3. Essen-Møller <sup>61</sup>	Bilateral ovariectomy; period of gestation, fourth week	Delivered at full term (260 days), after operation
4. Rausch, Z. Weifel <sup>38</sup>	Bilateral ovariectomy, 43 days of gestation	Aborted 15 days post-operative
5. Schoekaert, R. <sup>39</sup>	Bilateral ovariectomy, fifth month gestation	Full term, normal delivery
6. E. Levy-Solal <sup>40</sup>	Bilateral ovariectomy, ninth month gestation	Cesarean section successful
7. Faure, J. L. <sup>41</sup>	Bilateral ovariectomy, 6 weeks' gestation	Full term, normal delivery
8. Notes, Bernard <sup>1</sup>	Bilateral ovariectomy, 3½ months' gestation	Labor induced successfully 2 weeks before full term
9. Wells, H. Brooks <sup>43</sup>	Bilateral ovariectomy, 4 months' gestation	Term
10. Campbell, Malcolm <sup>44</sup>	Bilateral ovariectomy, third month	Full term normal delivery
11. Campbell, Malcolm <sup>44</sup> (Case of Thornton Knowsley)	Bilateral ovariectomy in fourth month	Full term 5 mo. 19 days after operation
12. Eiss, Stanley <sup>19</sup>	Bilateral ovariectomy, fourth month	Normal childbirth
13. Wilson, Karl M. <sup>6</sup>	Removal of only ovary present in patient at 5 weeks	Abortion 5 days after operation
14. Waldstein <sup>23</sup>	Bilateral ovariectomy two months	Term
15. Matthews, Frank S. <sup>45</sup>	Case 1, removal both ovaries and uterus, 1 month	Surgical abortion
16. Levy, Suzanne <sup>47</sup> (Case of J. L. Faure) Obs. 1	Bilateral ovariectomy, third month	Full term, normal delivery
17. Idem. (Case of M. Faure) Obs. 2	Bilateral ovariectomy, third month	Full term, normal delivery
18. Idem. (Case of Galabin) Obs. 5	Bilateral ovariectomy, fifth month	Full term
19. Idem. (Case of Mangin) Obs. 6	Bilateral ovariectomy, second month	Delivery at full term

TABLE I

AUTHOR	CASES OF BILATERAL DERMOID CYSTS	COMPLICATING PREGNANCY
1. Bantock <sup>35</sup>	1	Yes
2. Kosminski <sup>36</sup>	1	Yes
3. Nystrom, E. <sup>37</sup>	1	Yes
4. Rauseh, Z. W. <sup>38</sup>	1	Yes
5. Schoekaert, R. <sup>39</sup>	1	Yes
6. Levy-Solal, E. <sup>40</sup>	1	Yes
7. Faure, J. L. <sup>41</sup>	1	Yes
8. Notes, Bernard <sup>1</sup>	1	Yes
9. Gellhorn, George <sup>42</sup>	1	Yes
10. Wells, H. Brooks <sup>43</sup>	1	Yes
11. Manton, W. P. <sup>3</sup>	1 of his own, 19 be- fore 1911 from lit- erature	Yes (but diagnosed after delivery) 9 mo.
12. Campbell, Malcolm <sup>44</sup>	1 of his own 1 of Page, F. 1 of Thornton Knowsley 1 of Mattei 1 of Schroder 1 of Terrier	Yes Yes Yes Yes Yes Yes Yes
13. Waldstein <sup>23</sup>	1	Yes
14. Matthews, Frank S. <sup>45</sup>	4	Yes
15. Campbell <sup>46</sup>	1	Yes
16. Levy, Suzanne <sup>47</sup>	1	Yes
17. Idem. Case <sup>48</sup> of M. Faure, reported as "Obs. 11"	1	Yes (full term)
18. Idem.	1	Yes
19. Idem. Case of Munde, Obs. S	1	Yes
20. Runeskog, B. <sup>49</sup>	1	Yes
21. Abruzzese, C. <sup>50</sup>	2	Yes
22. Duncan, Perry E. <sup>51</sup>	1	Diagnosed 4 mo. after abortion
23. Stropeni, L. <sup>52</sup> (Cases of Horr- mann, 1911)	1 2	Yes Yes
24. Loewy, R., and Gueniot, P. <sup>53</sup> Case of Chantreuil <sup>54</sup> Case of Flaischen (1892) Case of Galabin <sup>55</sup> Case of Braum (1892) Case of Mangin <sup>56</sup> Case of Merse (1896) Case of Cortiguera (1895)	1 1 1 1 1 1 1	Yes Yes Yes Yes Yes Yes Yes
25. Deletrez <sup>57</sup>	1	Yes
26. Delporte <sup>58</sup>	1	Yes

conclusions relative to bilateral ovariectomy performed during gestation, so we decided to investigate the available literature on this point. We found that removal of both ovaries in the early months of pregnancy is a comparatively uncommon occurrence and slightly more unusual is the continuance to term of the pregnant woman in whom a bilateral oophorectomy has been done in the third month of pregnancy. In addition to our case, 12 in the first three months' gestation, in which bilateral oophorectomy was done, are described in the available liter-

TABLE III. TIME OF OPERATION AND OUTCOME

	MONTH	CASES GIVEN	ABORTIONS
Part 1:	Taken from McKerron <sup>22</sup> and concerns cases in which corpus luteum was removed		
	Second	5	18.5%
	Third	5	8.8%
	Fourth	3	5.3%
	Fifth	2	6.2%
	Sixth	4	22.2%
	Seventh	3	20.0%
	Eighth	4	57.1%
	Ninth	0	0.0%
Part 2:	Taken from M. Erik Ask-Upmark <sup>27</sup> and concerns cases of corpus luteum removed		
	First and second	16	25.0%
	Third	18	11.0%
	Fourth	17	12.0%
	Fifth	14	28.0%
	Sixth	2	50.0%
	Seventh	2	50.0%
	Eighth	8	25.0%
Part 3:	Taken from Table II of this paper (bilateral ovariectomies)		
	First and second	6	33 $\frac{1}{3}$ %
	Third	7	14 $\frac{2}{7}$ %
	Fourth	7	0.0%
	Fifth	3	33 $\frac{1}{3}$ %
	Sixth	2	50.0%
	Seventh	1	100.0%
	Eighth	0	0.0%
	Ninth	1	0.0%

nancy. Briefly stated, the possible complications are: the dangers of cysts becoming malignant epitheliomas during pregnancy;<sup>18</sup> the greater danger of torsion of the pedicle and gangrene of the cysts in gravid women;<sup>18</sup> suppuration of the tumors;<sup>18</sup> mechanical interference with labor;<sup>21</sup> malpresentation and uterine inertia;<sup>24</sup> hemorrhage into the tumor;<sup>24</sup> rupture of dermoids with an associated chemical peritonitis.<sup>23, 20</sup> Since there is a possibility of the occurrence of any or all of these complications at any time during gestation and since it is not endocrinologically necessary (see discussion later), we do not agree with that small minority of authors who maintain that ovariectomy should be done at term and the patient delivered from below subsequent to the operation.<sup>25</sup> The results noted in the tables convince us that, as to the treatment in the early months, we agree with Frank;<sup>26</sup> namely, it is better to postpone laparotomy and removal of the dermoids until after the corpus luteum (at least four to six weeks) is no longer necessary, unless an acute surgical condition demands an immediate operation. Study of results warrants the conclusion that the fourth month is the optimum time for surgical treatment. This is in accord with the conclusion of Levy,<sup>18</sup> of McKerron,<sup>22</sup> and of Lynch.<sup>20</sup> If the diagnosis is made shortly before viability, the evidence recommends "watchful waiting" until the fetus becomes viable, at which time operation is accompanied by cesarean section. Thus, the paramount question in surgical treatment concerns time and type of operation.

Concerning the type of operation, we believe that ovariectomy or resection is best decided at the time of laparotomy. The ideal, of course, is to conserve as much normal ovarian tissue as possible. There is a divergence of opinion relative to the removal of the tubes. Some believe this is more likely to cause abortion. This was not true in our case, and we believe that the oviduct should be removed

TABLE II—CONT'D

AUTHOR	PERIOD OF GESTATION AT WHICH OPERATION WAS PERFORMED	OUTCOME OF PREGNANCY
20. Idem. (Case of Bernard) Obs. 7	Bilateral ovariectomy, third month	Aborted fourth post-operative day
21. Idem. (Case of Munde) Obs. 8	Bilateral ovariectomy, 6 months	Aborted
22. Idem. (Case of Sutton)	Bilateral ovariectomy. Gestation not given	Twins at term
23. Idem. (Report of Perier on case of Mouchet) 1897	Bilateral ovariectomy	
24. Idem. (Case of Polailon)	Bilateral ovariectomy, 4 months	Full term normal delivery, normal child
25. Idem. (Case of Bankock, from Rev. de Pozzi, Obs. 4)	Bilateral ovariectomy, 3 months	Full term
26. Idem. Braun (Case in Rev. de Pozzi) Obs. 9	Bilateral ovariectomy, 5 months	Aborted fourteenth day postoperative
27. Idem. (Case of Cortiguera in Rev. de Pozzi)	Bilateral ovariectomy	Aborted
28. Idem. (Case of Merse in Rev. de Pozzi)	Bilateral ovariectomy, ninth month	Full term, normal
29. Polichetti, E. <sup>50</sup>	Bilateral ovariectomy, 6 weeks' gestation	Full term, normal delivery, normal fetus
30. Loewy, R., and Gueniot, P. (Case of Flaischen) <sup>53</sup>	Bilateral ovariectomy, third month of gestation	Full term, normal delivery and fetus
31. Galabin <sup>55</sup>	Bilateral ovariectomy	Not full term
32. Deletrez <sup>51</sup>	Bilateral ovariectomy, fourth month	Full term
33. Stropeni, L. <sup>52</sup> (Cases of Horrmann) (2)	1. Bilateral ovariectomy, second month	Aborted
	2. Bilateral ovariectomy. Period of gestation not given	Full term
Stropeni	Bilateral ovariectomy, fourth month	Full term, normal

ature; 10 delivered normally; 2 aborted. As a basis for our conclusions on surgical treatment we present Table II, showing the source, the month of gestation at which operation was performed, and the outcome of the pregnancy. These cases are grouped not because of their common etiology, but because each had surgical treatment, bilateral ovariectomy, performed during pregnancy.

## DISCUSSION

Possible complications of bilateral dermoid cysts have led to a more or less general agreement among obstetricians that the cysts should be removed during preg-

quantities of progesterone too small to produce pregnanediol in quantities sufficiently large to be determined by the method employed. They further state that the placental production of progesterone, at least in one case, begins about the second month, i.e., about the time (sixtieth day) that Browne and Venning<sup>10</sup> and later Evans and others<sup>11</sup> found the maximum gonadotropic substance occurs in pregnancy. Obviously, the appearance of such large quantities in pregnancy, at a time when the ovaries can be removed in the human being without miscarriage (Tables II and III) further supports the conclusion that progesterone is not only found in the placenta, but it is elaborated in it. This is not in accord with the findings of Collip and Campbell,<sup>13</sup> who believe they have shown that the placenta does not produce a corpus luteum hormone but that it manufactures three other hormones: (1) one corresponding to folliculin; (2) one corresponding to the so-called prolan A, and (3) one corresponding to prolan B.

The outstanding difficulty met in these investigations concerning the chemistry of the maintenance of pregnancy is that the tests used most frequently in the clinical practice are urine tests for the metabolic product of the hormone, pregnanediol glucuronide, rather than for the specific hormone content of the blood. Hamblen and associates (1939) list in detail the four factors which are concerned in the excretion of pregnanediol, thus complicating the interpretation of urinary findings. Allen (1939) reports a new and more sensitive method for the bio-assay of progesterone, based upon blood specimens.<sup>31</sup>

We believe the above experimental evidence points to the placenta, after sixty days, as the chief custodian of the preservation of pregnancy endocrinologically in the human being. This does not clear up the rationale of using progestin in the case of threatened abortion for its pharmacologic action (uterine sedation) or as a possible adjunct to an inadequate corpus luteum in the early months of gestation, or as a possible adjunct to an inadequate placenta after sixty days of gestation. Experimental evidence in animals would suggest that in the case of the last, estrogen should be given with progesterone. Before this type of therapy can be scientifically administered, more studies are needed during pregnancies to determine the normal for blood and for urine at stated time intervals.

A start in this direction has been made by Stover and Pratt,<sup>33</sup> 1939, and Rakoff,<sup>34</sup> 1939. Likewise, once the normals are determined, urinary and blood studies on patients with threatened abortion may serve as a guide to the administration of progesterone and estrogen and their indications in threatened abortion be clarified. The advantage of progesterone over other uterine sedatives is at this time questionable; not to mention comparatively expensive.

These studies might help to solve the riddle of pre-eclampsia, since the excretion of pregnanediol has been reported to be low in such patients (Weil, 1938; Smith and Smith, 1938); although the explanation may lie in liver dysfunction, one of the factors involved in the findings of Hamblen and others,<sup>32</sup> 1939.

To continue with the endocrine implications of the case reported by us, the precipitous labor of our case would suggest that folliculin in the mechanism of normal labor may not be necessary in human beings, or it may be supplied by some other organ. These observations are in keeping with the experimental findings of Collip and Campbell,<sup>13</sup> namely, that the placenta manufactures a hormone corresponding to folliculin. We were unable to ascertain the normalcy of lactation in many of the cases of bilateral oophorectomies reported in the literature. Lactation was spontaneously absent after the fifth day post partum in our case. We wish to emphasize that this in no way essentially contradicts the findings of S. Levy,<sup>18</sup> that in spite of double castration the puerperium may be normal.

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if chronically diseased or if double ovariectomy is done. We were not able to find in the literature available to us sufficient evidence of tube removal causing abortion to justify our leaving them routinely.

It is interesting to note in passing that Pucel<sup>28</sup> and Heils<sup>29</sup> report 16.5 per cent and 19.47 per cent of abortions, respectively, following operative procedure, while Remy<sup>30</sup> finds 17 per cent abortions without any operative interference whatever. The dangers of complications outweigh the dangers of abortion if these findings justify any conclusion.

Let us consider next the endocrinologic aspects of management. We have implied above that the corpus luteum played a part in our conclusion as to the optimum time of operation. A review of recent articles concerning this gland will show us why this is true, and possibly what endocrine therapy is needed postoperatively to encourage a normal gestation and delivery.

According to Wolf,<sup>4</sup> the luteinizing function in the human being is maintained after the first half of pregnancy solely by the placenta and the pituitary and injections of progesterin can prevent habitual abortion by keeping the uterine musculature quiet. This is in keeping with the classical observations of Fraenkel, Loeb, and Ancel and Bouin, which established the corpus luteum as an endocrine gland whose primary function was to prepare the uterus for implantation of the fertilized egg.<sup>31</sup> Wilson<sup>6</sup> sums up the evidence in human beings by saying: "While in general the corpus luteum is necessary for the proper maintenance of pregnancy in the early months, the duration of the time that this necessity exists varies with individuals." Individual variations are always a safe hypothesis in medicine never to be minimized; but for practical clinical purposes we attempt to arrive at the general normal for the initial approach to treatment or management and to subsequently individualize it. Pratt,<sup>7</sup> commenting on Wilson's paper, describes one clear-cut illustration of a normal human pregnancy without the presence of a corpus luteum after the beginning of nidation (twenty-one days after onset of patient's last menstrual flow). Pratt and others<sup>8</sup> state: "Indications for the therapeutic use of progesterin for treatment of abortion are theoretically speculative."

That the placenta and corpus luteum contain the same hormone has been proved, for recently progesterin has been found in human placenta (Mazer and Goldstein, 1932; Adler, de Fremery and Tausk, 1934; Ehrhardt, 1934; McGinty, McCullough and Walter, 1936; Ehrhardt and Fischer-Wasels, 1936; Smith and Kennard, 1936<sup>31</sup>). The progestational substance has been extracted from the original extract which also contained an estrogen fraction (Allen and Myer, 1933) and the structural formula of progesterone ascertained (Butenandt, May, 1934; Slotta, Ruschig and Fels, July, 1934; Allen and Wintersteiner, August, 1934; and Hartmann and Wettstein, 1934<sup>31</sup>). The performance of bilateral ovariectomy with noninterference with gestation and delivery fits in with the concept of the presence of progesterin in the placenta.

It was shown by Allen, 1930, Hisaw and Leonard, 1930, that the previous influence of the estrogenic hormone was needed to make it possible for progesterone to produce its progestational changes in the endometrium. This synergistic action of estrogen and progesterone is further shown by the more recent experiments of Allen and Heckel. Their work makes it evident that for progesterone to have any visible effect on the structure of the uterus, it must be given to an animal which has recently been under the influence of estrogen, and if its effects are to be maintained for more than a short time, estrogen must be given with progesterone. The efficacy of progesterone, or of progesterone and estrogen in combination, in maintaining human pregnancy, has not been extensively or thoroughly investigated.<sup>31</sup>

Jones and Weil<sup>9</sup> report a case in which the corpus luteum was removed on Oct. 28, 1937, and who subsequently delivered a normal, living child on June 27, 1938. In this case they observed that no pregnanediol was present in the urine for about twelve days after removal of the corpus luteum. It then reappeared in increasing amounts. Their conclusion was that pregnancy can survive in the human being after the withdrawal of progesterone, or that it can survive on

# STUDIES ON PRESERVATION AND USE FOR TRANSFUSION OF PLACENTAL BLOOD

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THE therapeutic use of blood transfusions plays an important role in modern medicine, particularly in the emergencies of obstetrics. Suitable donors, however, are not always available, so that attention was focused on the problem of the preservation of human blood and following diligent investigation, particularly by the Russians, the modern blood bank has been evolved.

In 1938, Goodall and his co-workers reported a method of collecting and preserving placental blood with its subsequent use for transfusion in adults. The reported results sounded like the actual fulfillment of every obstetrician's dream. By using the blood preservative of the Moscow Institute of Hematology, Goodall reported that the blood could be kept practically indefinitely and given without fear of any reaction and, moreover, he assumed the biologic significance of fetal blood to be even greater than that from adult donors. Subsequently, several other clinics have attempted to confirm Goodall's results, and although the procedure seemed to have possibilities, their enthusiasm apparently did not equal Goodall's.

The procedure has been given a careful test at the Baltimore City Hospitals. On the Obstetrical Division, about 200 service cases are delivered each month in the hospital so that ample clinical material was available.

## METHODS AND RESULTS

We repeated the method of collection as described by Goodall; that is, by milking the blood out through the sterilized severed end of the cord into a sterile flask which contained the preservative solution—the placenta remaining in utero. Those cases in which the child was premature, the membranes prematurely ruptured, the uterine cavity infected or the blood Wassermann reaction positive, were not used. The average amount of blood collected from such selected placentas was 70 c.c., although Goodall reported an average of over 100 c.c. A specimen of blood was also collected in two separate tubes for grouping and Wassermann tests. The flasks were stored in an ice box with a constant temperature of 36° F. Eight specimens were immediately cultured upon collection. These cultures were done on beef heart infusion agar (pH 7.8) poured plated and on beef heart infusion peptone broth (pH 7.6). These cultures were all negative and the same specimens proved to be negative on re-culture five days later on the same type media. In order to determine the bactericidal action of the preservative, original specimens known to be negative were intentionally contaminated with *Bacillus coli*, *Staphylococcus albus*, *Staphylococcus aureus*, and *Bacillus subtilis*. These specimens were kept in the ice box for four days and recultured. Those flasks containing *Bacillus coli* or *Staphylococcus albus* were sterile. *Staphylococcus aureus* was inhibited, but *Bacillus subtilis* flourished in the mixture.

At this stage of the work, it seemed safe to use the blood for transfusion so far as the bacteriologic evidence was concerned. Accordingly, 4 transfusions

\*With the technical assistance of Arthur Ballantyne.

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## 605 MEDICAL ARTS BUILDING

Munoz, Hector Cruz: *Hyperplasia of the Endometrium Following Operative Procedures on the Ovary*, *Bol. Soc. chilena de obst. y ginec.* 4: 71, 1938.

The author reviews the literature and reports two cases of hyperplasia of the endometrium following operative procedures on the ovary. He concludes that the gynecologic operations which more or less considerably reduce ovarian tissue may produce hyperplasia of the endometrium with typical hemorrhage. The anatomic alterations found in these cases are identical with those encountered in laboratory animals.

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certain. The amount of blood given could not be considered as a cause. Reactions were obtained in some cases when only 60 c.c. of blood had been given and the transfusion had to be stopped. One patient received 400 c.c. of blood at one time without a reaction. The patient was a Group II, with a ruptured uterus. She was given approximately 200 c.c. of her own group and 200 c.c. of Group IV, immediately after the Group II blood had run in.

Four patients received more than one transfusion. One of these received 3 and had 1 reaction, 1 received 2 and had reactions with both, and the third had 3 transfusions, with reactions in two instances. The fourth received 2 transfusions without reaction.

The cross matching was checked carefully by 3 different individuals. In order to establish a control regarding the preservative, 6 patients were given sterile preservative, without blood, intravenously and none of them had a reaction. This procedure was carried out in the same fashion as when blood was collected. The flasks were unwrapped from the sterile towel; opened, as if they were going to receive blood; plugged after an interval equal to the time it would take to collect the blood. It was then stored in the ice box for various intervals and then given to the patient. In 2 cases, preservative was given without untoward effect to patients who had had a reaction with placental blood.

Further studies were made in an attempt to ascertain the cause of reactions. Five transfusions of approximately 100 c.c. of blood from adult donors and 125 c.c. of the above preservative were given to patients and in only one a slight reaction occurred.

For control purposes, when feasible, the contents of one flask were used for transfusion as we were anxious to observe the effects of storage, hemolysis, etc. When several flasks were used, the bloods used were as nearly as possible similar as to storage time, hemolysis, etc.

The hemoglobin rise in most cases was satisfactory. The average rise was 7 per cent in three days and at the end of five days, the average rose to 11 per cent. However, these figures are not conclusive, as the amounts given varied somewhat. Phenomenal rises occurred in some cases; in one instance a 20 per cent increase was noted on the third day. And by the fifth day, 3 patients, excluding the above, had had an increase in hemoglobin value as much as 22 per cent. It is difficult to correlate the increase in hemoglobin values with the hemoglobin content of the placental blood, red blood count, the time of storage, and other factors in such a small series. But we can say with reasonable certainty that this blood does give a satisfactory rise in hemoglobin value and in some cases it is phenomenal. Perhaps the correction of the dilution phenomena of pregnancy during the puerperium may play some part.

Although we had previously satisfied ourselves as to the sterility of the blood given at this stage, we felt that this should be checked once more in view of the number of reactions. Consequently, immediately before giving a transfusion, a small amount of blood was transferred to a small sterile flask for culture on the same media as previously used. Seventeen consecutive cultures were sterile. Reactions occurred in 25 per cent of these 17.

Recent investigation by DeGown and others, indicates the advantages of a modified Rous-Turner preservative consisting of: 5.4 per cent glucose, 13 parts; 3.2 per cent sodium citrate, 2 parts; and blood, 10 parts.

We collected blood in the usual fashion and gave 6 transfusions using this solution as a preservative, removing samples as usual for culture immediately before giving the blood. The minimum time that this blood had been stored was one day, and maximum five days. None of these patients had reactions, but within twenty-four hours, we had luxuriant growths of *Bacillus fecalis alkaligenes*, 30 to 100 colonies per c.c. The blood had been planted on the same media as used previously, beef heart infusion agar poured plates and beef heart infusion peptone broth. These patients were watched carefully but all of them had normal temperature curves during their hospital stay. They were checked again one month after leaving the hospital and all felt well.

We, of course, then ceased giving transfusions but still collected blood, trying to perfect our technique. Seven per cent iodine was substituted for the mercuric

were given to patients who were afebrile but who had low hemoglobin values postpartum, in amounts ranging from 150 to 250 c.c. All 4 patients had severe reactions which took the form of a chill followed by a temperature rise to 103° or 104° F., pain in the back and extremities. In 1, the reaction set in before all the blood was given. In the other 3, it occurred within an hour of receiving the blood.

Since our yield was quite small and we had 4 consecutive reactions and thinking that perhaps certain unknown substances had passed into the blood while collecting it, we devised another method for collection. As soon as the child was born, the cord was clamped immediately as close as possible to the umbilicus and was severed between two clamps. The placenta was then expressed and was placed on a sterile towel on the instrument table. The cord was then milked down to within about 5 cm. of the base of the placenta and clamped once more. The cord and a portion of the placenta adjacent to it were cleansed with a mercuric chloride, or Scott's solution followed by alcohol. A sterile towel was placed over the clamp and empty cord adjacent to it. If the operator was collecting the blood, he would change his gloves. A No. 16 needle, to which was attached a two-way stopcock and a 50 c.c. or 100 c.c. sterile syringe, would then be inserted into the main vessel of the cord and the blood drawn into the syringe. The blood collected was then transferred to a sterile flask containing the preservative, a small amount being placed in an oxalate bottle for blood counting, hemoglobin determination, etc. The two-way stopcock was utilized to prevent the blood from escaping from the end of the inserted needle while it was being transferred. Only slight suction was necessary in order to draw the blood into the syringe. By this method, our yield averaged 87 c.c. It was advantageous from 2 aspects. One could inspect the placenta and by the size of the vessels and the placenta could determine whether the yield would be worth while. Second, by this method, the operator did not necessarily have to collect the blood, as someone standing by who knew the method could don a pair of sterile gloves and carry out the same procedure.

The majority of placentas used were those which were thought would give a greater yield than 70 c.c. However, included in our collections were some yields of 50 c.c., utilized when a large number of deliveries were productive of small placentas, and we were anxious to obtain blood.

Transfusions were then given in amounts ranging from 65 to 400 c.c. The preservative solution used was that devised by the Moscow Institute of Hematology, consisting of:

Sodium chloride	7.0 gm.	} in 1,000 c.c. of distilled water. The amount of preservative used was 125 c.c.
Sodium citrate	5.0 gm.	
Potassium chloride	0.2 gm.	
Magnesium sulphate	0.04 gm.	

Thirty-six transfusions were given to adults with reactions similar to the above in 47 per cent of the cases. Six transfusions were also given to infants and children on the pediatric service with a questionable reaction in one. It was questionable because the patient had otitis media and pneumonia and was receiving sulfapyridine. On analysis the reactions could not be correlated with any controllable factor such as length of preservation, amount of blood and preservative, amount of hemolysis, speed of administration, or blood groups. Analyzing this in somewhat greater detail, the length of storage before giving the transfusions varied between one and twenty-four days (average six days). This made no difference whatsoever in this small series. Hemolysis was not a factor. Some of the bloods given were markedly hemolyzed and no reactions occurred. In fact, we noted that with this solution and others that we used, the rate and amount of hemolysis were variable factors. Hemolysis in some of the above blood used occurred in about twenty-four to forty-eight hours and in others, somewhat later. It was not referable to any appreciable extent on the ratio between the amount of blood and the preservative. Whether it was dependent on an individual variation of the cells themselves, it is difficult to be

Moscow solution as a preservative, stored for two or three days and then cultured. Positive cultures of *Bacillus fecalis* were obtained in all 6.

Grodberg and Carey recently reported a series of 75 transfusions with placental blood at the Boston City Hospital. Their method of collection was similar to that of Goodall except for some minor details. They reported that very few of their bloods collected gave positive cultures. At the time of collection, a sample of blood was cultured on plain broth, without glucose, similar to our original cultures.

It was thought at this time that perhaps the passage of the placenta through the vagina and the handling of the placenta in some fashion increased the number of bacteria in the blood. We were also anxious to collect blood in a similar manner as was done in Boston and to see whether by our new medium positive cultures could be obtained. Accordingly we collected ten samples of blood from the cut end of the cord, cleaning the cord with iodine and alcohol and severing it with sterile scissors. Culturing these collections with the new medium, we obtained positive cultures of *Bacillus fecalis* in 9 out of 10. The preservatives used were 20 c.c. of 5 per cent sodium citrate in 5 and 50 c.c. of 1.5 per cent sodium citrate in normal saline in the other five. We must say, however, that growth was moderate and took twenty-four to forty-eight hours to appear on the plates. The blood was kept in the refrigerator from two to three days before planting it on the medium—average collection was 81 c.c.

Samples of blood stored for various intervals which were originally positive were now cultured once more. Six samples of blood were found to be sterile seven days after they were found to contain organisms. Others cultured ten, twelve, and sixteen days after being found positive were also sterile. The preservatives in the above were equal numbers of the various types. Moscow, 5 per cent sodium citrate, and 50 c.c. of 1.5 per cent sodium citrate in normal saline. Equal numbers of those collected by needle and syringe, and by the method of Grodberg and Carey, were sterile. It is quite possible that the blood was sterile a few days before we cultured it. In our previous studies *Bacillus coli* and *Staphylococcus albus* were apparently killed in four days.

Eight transfusions were then given in amounts ranging from 100 to 120 c.c., using blood which had previously contained organisms and now had been found to be sterile. The minimum time of storage was thirteen days, maximum twenty days. Preservatives used were 5 per cent sodium citrate, 20 c.c. and 50 c.c. of 1.5 per cent sodium citrate in normal saline, four of each. One severe reaction was obtained with a chill lasting twelve minutes and a temperature rise of 103° F. The blood used in this case had been stored thirteen days and was collected by the method of Grodberg and Carey. Observations on hemolysis revealed that the best preservative from this standpoint was the 1.5 per cent sodium citrate in normal saline. Hemolysis was slight with this preservative as long as twenty days after collection. The next best was 5 per cent sodium citrate solution, followed by the Moscow preservative and then glucose citrate mixture. There was, however, very little to choose between the latter two preservatives; both hemolyzed the blood much more rapidly than the first two mentioned.

An attempt was now made to determine the source of the organisms. Blood and surface cultures were taken from various portions of the placenta—6 placentas were used. The procedure was as follows: Immediately after delivery the cord was clamped as usual. It was then cleansed with iodine and alcohol. The cord was cut with sterile scissors and blood collected for culture. The cord was then clamped once more. It was cleansed again and a surface culture obtained. A needle was then inserted into one of the veins between two clamps and another sample of blood was obtained. The placenta was then expressed. The cord was clamped immediately about 3 or 4 cm. from its origin from the placenta. The surface of the cord where a needle was to be inserted and the adjoining placenta was cleansed as usual and another surface culture was taken from this area. A needle was then inserted, and another sample of blood withdrawn.

Our results were similar in all 6 placentas used. All surface cultures, taken before the cord and placenta were cleansed, yielded *Staphylococcus aureus*, *Staphylococcus albus*, and *Bacillus coli* with the exception of one, in which no growth

chloride without any effect. Seventeen consecutive cultures, with the glucose citrate as a preservative, were positive for *Bacillus fecalis alkaligenes* with the number of colonies ranging from 15 to 200 per c.c. The time interval between collection and culturing varied from twelve hours to five days, average forty-eight hours. Hemolysis was quite marked with this preservative, usually occurring in twenty-four hours and gradually increasing. With this solution and with our previous solution, clotting also occurred to some extent, but this was a variable phenomenon as to time and amount.

Our conclusion was that the glucose enhanced the growth of these organisms, and we then decided to use 15 c.c. of a 5 per cent sodium citrate solution as a preservative and carry out further cultures, using 7 per cent iodine and 95 per cent alcohol to clean up the cord. Six samples of blood were then collected and cultured with the previous media and one positive culture was obtained; the rest were sterile. No reactions were obtained, using this blood in amounts ranging from 95 to 100 c.c. The blood was given after a storage time of three to four days. Hemolysis was slight in this period of time, but the blood was very thick so that it was necessary to dilute it with normal saline in order for it to pass through a sterile gauze filter. One patient received blood which subsequently grew organisms. The reason that this blood was used was due to the fact that we had had such rapid growth with the glucose solution, usually in twelve to fourteen hours, that we thought that if the bloods were positive for this organism it should appear in at least twenty-four hours. No growth had occurred with any of these blood samples in twenty-four hours; we then went ahead and transfused the 6 patients mentioned, only to find out that on the following day, colonies had begun to appear in the one culture.

At this stage, it was apparent that the glucose had enhanced the growth of these organisms and that the preservative was an excellent medium. We were now anxious to know what, if any, of the constituents of the Moscow solution would have a bactericidal or bacteriostatic effect and counteract the presence of glucose.

A solution consisting of 5.4 per cent glucose, 13 parts, and 3.2 per cent sodium citrate, 2 parts, was made up and to a liter of this was added 0.04 gm. of magnesium sulphate and 0.2 gm. of potassium chloride—the same amount of these constituents as was present in the Moscow solution. We had omitted sodium chloride and changed the proportion of sodium citrate.

Six consecutive blood samples were then collected carefully in the usual fashion, using iodine and alcohol to clean up the cord, and all 6 were positive for *Bacillus fecalis* in less than twenty-four hours. These had all been stored previously in the refrigerator from two to four days.

The problem that now confronted us was how to obtain sterile blood. It also occurred to us that perhaps originally, with the Moscow solution and the 5 per cent sodium citrate solution, positive cultures would have been obtained had we used glucose in the media. Consequently, we began to culture all collections with a special medium consisting of (1) beef heart priptose agar which contains 1 per cent glucose (pH 7.3) and (2) beef heart protease agar (pH 7.2). With the latter, when pouring the plates, 2 c.c. of a sterile 10 per cent glucose solution were added. In addition, cultures were also made with beef heart infusion protease broth (pH 7.4), containing 1 per cent glucose.

We then collected twelve samples of blood. In 6 of these, the preservative used was 20 c.c. of a 5 per cent sodium citrate solution and in the remaining six 50 c.c. of a 1.5 per cent sodium citrate solution in normal saline. Not knowing the exact source of these organisms and attempting to eliminate contaminants from the surface of the cord, that portion where the needle was to be inserted as well as a portion of the surrounding placenta was cleansed vigorously with green soap, ether, alcohol, and 7 per cent iodine, followed by alcohol once more. These samples were stored for two to four days, and then cultured with the new medium and all were strongly positive for *Bacillus fecalis alkaligenes*. In fact, in 6 of these, in addition to the above clean up, concentrated nitric acid was applied to the area where the needle was to be inserted and then washed off with alcohol, without any better results. Six samples of blood were also collected, using the

## SUMMARY

1. Hematologic studies on placental blood revealed that such blood would be desirable for adult transfusion if it could be collected sterily, in sufficient quantities, and satisfactorily preserved.

2. An attempt was made to confirm the work of previous investigators who claimed placental blood could be adequately collected and preserved and subsequently given as transfusions to adults with a minimal number of reactions.

3. By using the usual bacteriologic culture media placental blood could apparently be collected and preserved sterily, but the subsequent transfusion of these specimens was accompanied by a high percentage of reactions.

4. A comparative study of several different preservative solutions indicated that a 1.5 per cent sodium citrate in normal saline is the most desirable solution.

5. Further bacteriologic studies, using special culture media, revealed that a high percentage of the collected blood was actually contaminated. Several modifications of the method of collection did not eliminate such contamination.

6. Transfusion reactions could not be correlated with bacterial contamination or any other detectable factors such as amount of hemolysis, type of preservative, time of storage, etc.

## CONCLUSIONS

Our studies indicate that the biologic significance of placental blood is somewhat greater than adult blood. Theoretically, the use of placental blood for transfusion is attractive; however, the technical difficulties encountered in its collection and sterile preservation are sufficient to make its use impracticable under the present state of our resources.

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**Veiga de Carvalho, H.:** The Microscopic Picture of Syphilis of the Umbilical Cord and Its Significance in the Pathology of Gestation, Rev. de obstet. e ginec. de São Paulo 3: 211, 1938.

In cases of syphilis the lesions found in the umbilical cord were endoarteritis, endophlebitis, infiltration with inflammatory cells, adventitial infiltration, necrosis and thrombosis of vessels.

There also were changes in the intima of the vessels, which were characteristic. The author makes a plea for the histologic examination of all umbilical cords of babies born of syphilitic mothers to establish the condition of the child.

MARIO A. CASTALLO.

was obtained. All surface cultures taken after the cord was cleansed were sterile. Blood cultures whose sources were the cut end of the cord and from one of the veins before expression of the placenta yielded *Bacillus fecalis* in all. Blood cultures taken after the expression of the placenta also grew *Bacillus fecalis*. In the latter, growth was heaviest.

The indication was that the blood from these 6 placentas used, and most likely all the others, contained these organisms and that contamination did not occur by handling, etc. We realize that this is a startling statement to make yet we are forced to come to this conclusion. All our bacteriologic work was done carefully and all blood cultures were controlled by always planting sterile adult blood kept in the laboratory on the same medium as was used to culture placental blood. It certainly was not a laboratory contaminant, as it would have been obtained in other cultures. We cannot explain why we did not obtain *Bacillus fecalis* from the surface of the uncleansed placenta and cord. Most likely we would have obtained the organism if we had cultured more. It is surprising that this organism should always be present. In fact, some of the blood was cultured in another laboratory in the city, and also yielded the same organism. Samples of various preservatives were also cultured after autoclaving storage, etc., but were sterile.

Studies on the reactions of the preservatives alone and in combination with blood were also done.

TABLE I

	pH WITHOUT BLOOD	pH FRESH BLOOD AND PRESERVATIVE	pH BLOOD AND DEAD BACTERIA
Moscow preservative	7.4	8.5	8.9-9.0
Glucose-citrate	7.6	8.5	Bacteria could not be killed by storage
Sod. citrate 5%	7.5	8.4	8.8
Citrate-saline solution	7.5	8.4	9.0

It can be seen from our results that the pH certainly played no part as far as reactions were concerned. It can also be seen that the bacteria caused alkalization of the blood, and just by the addition of the blood to the preservative the pH rose. The reaction of the blood, we do not believe had anything to do with the cause of reactions. The similarity between the reaction of the Moscow preservative, the sodium citrate solutions, and the glucose solutions eliminates that as a factor.

Studies were also made on fresh placental blood with certified pipettes and counting chambers. Sahli hemoglobinometers, calibrated by O<sub>2</sub> capacity so that 100 per cent represents 14.5 gm. of Hg, were also used. The average hemoglobin value was 122 per cent on 60 consecutive samples; R.B.C. averaged 5 M; hematocrit 48 per cent; mean corpuscular volume 1 cubic micra; mean corpuscular hemoglobin content was  $34.0 \times 10^{-12}$  gm. hemoglobin.

The various blood types were in order of frequency, 4, 2, 3, 1 (Moss). Our results in the main agree with those of Grodberg and Carey who found that in 50 cases the baby's blood type had not changed on discharge. We, in addition, had the mothers bring the babies back several weeks after discharge. In two instances, we found that the placental blood had been Type IV (Moss) checked microscopically and macroscopically, and on checking the babies' types four weeks after discharge, we found that they were Type II. On going back over our records, we found that the placental blood in these two cases would not cross match with any of the patients who were also of Group IV, but did so with the patients who were Group II. We gave this blood without reaction to patients who were of the latter group. In these two instances, the baby's type was not checked at all during their tenure in the hospital. We interpret these results as meaning that occasionally placental blood is not type specific. However, we feel this to be of no practical significance since any incompatibility would be discovered in the cross matching between donor and recipient.

plasia cannot be made on the basis of the limited number of cases in the present series. The impression is obtained that progesterone therapy may prove of value if doses are given in a manner which as nearly as possible reproduces the normal corpus luteum output of progesterone. The present studies indicate that 5 mg. of progesterone is probably the minimal dose which will produce anatomic changes. However, smaller doses may produce symptomatic relief.

#### CASE REPORTS

CASE 1.—The patient, C. G., was a 17-year-old, nulliparous colored girl who was first seen in the dispensary May 10, 1938, complaining of irregular menses. Her menarche had occurred at the age of 16 years and had never been established regularly. The duration of the flow was from one to two weeks with profuse



Fig. 1.



Fig. 2.

Fig. 1.—(Path. No. 47979.) Low power photomicrograph of an endometrial biopsy taken after 50 mg. of progesterone administered in 5 mg. daily doses. There is no evidence of secretory activity in these glands, which show marked reduplication of the nuclei of the glandular epithelium.

Fig. 2.—(Path. No. 47651.) Low power photomicrograph of an endometrial biopsy taken after 50 mg. of progesterone administered in 5 mg. daily doses. There is beginning tortuosity of the glands, fraying of the cellular membrane at the luminal margin and a small amount of secretion in the lumen of the gland shown. The two cross sections of the glands show less activity, and one is slightly dilated, suggesting the previous hyperplastic pattern.

bleeding and no dysmenorrhea. Her present menstrual period had begun May 9 and the previous period had been from December 3 to 17. Physical examination revealed a very thin negress with normally developed puberal breasts, male hair distribution, slightly hypertrophied clitoris, and normal puberal pelvic organs.

As the patient was not bleeding profusely when first seen and her hemoglobin was 67 per cent, she was told to return before her next expected menstrual period for a suction curettage. She returned June 3 and an endometrial biopsy was taken at that time which showed endometrial hyperplasia. She failed to return for therapy and was next seen Jan. 17, 1939. At this time she gave a history of amenorrhea from May until October. Her October menstrual period lasted three weeks, and on January 2 she began to bleed again. This period was still

# THE HISTOLOGIC EFFECT OF PROGESTERONE ON HYPERPLASTIC ENDOMETRIA

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THE present investigation was undertaken to determine whether physiologic changes could be produced in endometria showing abnormal patterns. For this purpose seven cases of endometrial hyperplasia were studied. The criteria for diagnosing hyperplasia were: (1) Straight, dilated glands showing reduplication and overgrowth of the glandular epithelium. (2) Absence of secretory changes in the epithelial cells and the presence of basilar placed nuclei and intact luminal membranes. (3) Density of the stroma which is characterized by small, tightly packed stromal cells with very little cytoplasm and by the infiltration of lymphoid cells.

## MATERIAL

All seven cases in the present series were treated with synthetic progesterone\* and endometrial biopsies were obtained before injection. A suction curette was used and in order not to destroy the existing endometrial pattern, thorough curettements were not performed. Treatment was usually begun during a bleeding phase. In the majority of cases, 50 mg. of progesterone were given in 5 mg. doses over a period of ten days as described by Browne. Endometrial biopsies were again obtained at the end of treatment. Three cases showed no microscopic effect. Four cases showed secretory changes in the endometrium. However, in no case could the microscopic picture be mistaken for a normal secretory pattern. A persisting irregularity of the glands gave evidence of the former pathologic state (Figs. 2 and 5).

In 5 cases of the present series estrogen and pregnanediol determinations were made on forty-eight-hour specimens of urine before and after progesterone injections. Pregnanediol determinations were performed by the Weil technique as described by Bucher and Geschichter.† No patient was excreting pregnanediol when injections were begun. The progesterone was recovered as pregnanediol in only two instances. It is significant that one patient, although given 20 mg. of progesterone daily, showed no secretory changes in the endometrium, yet the largest amount of pregnanediol was recovered in this case. The estrogen determinations showed normal values except in two instances.

## RESULTS

In 6 patients a definite improvement in the bleeding symptoms was noticed. In 4 patients in whom injections were given over several months (Cases 2, 3, 5, and 7), fairly normal menses were established during treatment. However, since the condition is subject to spontaneous remissions and long periods of amenorrhea, an evaluation of progesterone therapy in cases of endometrial hyper-

\*The progesterone used in the present studies was proluton furnished through the courtesy of the Schering Corporation.

†It has been found impossible to prevent hydrolysis of the pregnanediol sodium glucuronide to the free form under collecting facilities which must necessarily be used with dispensary cases. For this reason determinations based on the recovery of free pregnanediol were used.



from April 6 to 12. April 25 to 28 she received 20 mg. of progesterone and did not bleed until May 5 to 10. She had a normal period June 4 to 9 and has not returned for an examination.

CASE 4.—The patient was a 27-year-old negress who was first seen Feb. 13, 1939, complaining of constant vaginal bleeding since January 9. Her previous menstrual period had been from December 2 to 7. She had had five pregnancies, the youngest child being 4 years old. Physical examination showed a normally developed, obese negress with normal pelvic organs. Her basal metabolic rate was minus six.



Fig. 3.—(Path. No. 48200.) Low power photomicrograph of an endometrial biopsy taken after the first series of progesterone injections (50 mg.). This section shows beginning tortuosity of the glands, and secretory droplets in the glandular epithelium.



Fig. 4.—(Path. No. 48333.) Low power photomicrograph of an endometrial biopsy taken after the second series of progesterone injections (50 mg.). Here the endometrial glands show more marked tortuosity and evidence of secretion in the glandular epithelium than shown in Fig. 3.

Therapeutic dilatation and curettage were performed and the diagnosis of endometrial hyperplasia was made. She had no further bleeding until April 20, when she began to hemorrhage and continued until seen in the dispensary May 11. Suction curettage at this time again revealed endometrial hyperplasia. A forty-eight-hour specimen of urine showed no pregnanediol and less than 10 rat units of estrogen per twenty-four hours. Progesterone was given May 13 to 23, 5 mg. a day, and bleeding continued throughout. A curettage May 23 showed secretory endometrium

present at the time of her dispensary visit. A second curettage again showed hyperplasia and she was given a course of progesterone injections, 5 mg. daily for ten days. Her bleeding continued although less profusely through the administration of the hormone. A curettage January 28, following 50 mg. of progesterone, showed no microscopic change in the endometrium (Fig. 1). She ceased bleeding January 30 and, although she was instructed to return in two weeks for a second series of injections, she failed to keep her appointment. When next seen she gave a history of a normal menstrual period in February, March, and April. She began to bleed profusely April 26 and was still bleeding May 3 when a suction curettage again showed hyperplasia.

CASE 2.—H. D. was a 22-year-old housewife with two children, the youngest being one year old. Her menses had begun at the age of 12 years and during the first year she had bled for eight days every two weeks. She then established a twenty-six to thirty-day cycle and was regular, except for the two periods of pregnancy, until two months before her visit to the hospital. At that time she had a menstrual period lasting fourteen days. Her last menstrual period had lasted from June 27 to July 8 with profuse bleeding. On physical examination the patient was an obese woman with poorly developed breasts (the patient stated she had been unable to nurse her babies). The pelvis was normal except for a retroversion of the uterus which could easily be replaced. The basal metabolic rate was minus six. A suction biopsy showed endometrial hyperplasia. As the patient's hemoglobin was 95 per cent, no therapy was given and she was told to report for observation after her next menstruation. This period was also prolonged and profuse, lasting from July 21 to August 3. She began to bleed again August 22 and bled through September 6. Pregnanediol determinations for September 19 and 20 were negative. September 21 a suction curettage again showed hyperplasia and she was given 50 mg. of progesterone from September 21 to 30. She failed to report for a check curettage. Her bleeding recurred October 18 to 29. November 4 a curettage again showed hyperplasia and she received a second course of progesterone from November 4 to 14. During this time she noticed slight vaginal bleeding on November 13. Curettage November 14 showed an interval secretory type of endometrium (Fig. 2). November 16, two days after cessation of progesterone, she began to bleed and bled moderately until November 25. She had an apparently normal period December 15 to 23 and when last seen in August, 1939, she had had no recurrence of excessive bleeding.

CASE 3.—This patient was first seen May 2, 1935, at the age of 14 years. At that time she gave a history of profuse menses since the age of 12 years and constant bleeding for nine months. Her hemoglobin was 44 per cent. Therapeutic dilatation and curettage were performed and endometrial hyperplasia was diagnosed. She remained comparatively free from symptoms until November, 1938, when she began to bleed and continued until Feb. 23, 1939, at which time she returned to the dispensary for treatment. Physical examination revealed a thin negress of 18 years with the male type of hair distribution and a moderately enlarged clitoris. Pelvic examination was negative. Basal metabolic rate was minus two and her hemoglobin was 52 per cent. A suction curettage February 23 showed endometrial hyperplasia. A forty-eight-hour urine specimen showed no pregnanediol and 30 rat units of estrogen per twenty-four hours. Progesterone was begun February 28 and her bleeding ceased March 2. She had a recurrence of spotty bleeding March 6 to 9, when progesterone was discontinued and a curettage showed secretory changes in the endometrium (Fig. 3). March 11, two days following cessation of injections, the patient began to bleed and continued in an apparently normal period until March 17. She returned March 28 and a forty-eight-hour specimen again showed no pregnanediol, but 80 rat units of estrogen per 24 hours. From March 30 to April 6 she received 40 mg. of progesterone and suction curettage on April 6 again showed secretory changes in the endometrium (Fig. 4). A forty-eight-hour specimen of urine, collected over the last two days of progesterone administration, failed to demonstrate any pregnanediol. There were 12 rat units of estrogen per twenty-four hours. The patient bled moderately

remained well over a period of three months after which bleeding recurred. Her last menstrual period had begun in the middle of October and when seen she was still bleeding. The only significant fact in her past history was that she had had a thyroidectomy at the age of 19 years for a nodular goiter without hyperthyroidism. Physical and pelvic examinations were negative. Her hemoglobin was 41 per cent and her basal metabolic rate was minus twelve.

A forty-eight-hour urine specimen showed no pregnanediol. A suction endometrial biopsy November 14 showed endometrial hyperplasia. On November 18 she was given 50 mg. of progesterone in four injections over a period of eight hours and total urine specimens were collected November 18 and 19. Four and seven-tenths milligrams of pregnanediol were recovered and 4.7 mg. were also recovered in a specimen collected November 20 and 21. Beginning November 22, she received 20 mg. a day of progesterone and total urine collections were made. No pregnanediol was recovered until November 26 and 27 at which time 2.8 mg. of pregnanediol were determined. November 28 and 29, 2.4 mg. of pregnanediol were recovered. The patient continued to bleed throughout the course of injections. A hysterectomy and biopsy of the right ovary were performed on November 30. The uterine endometrium showed hyperplasia and no evidence of secretory activity (Fig. 7). There were numerous follicular cysts in the ovary.

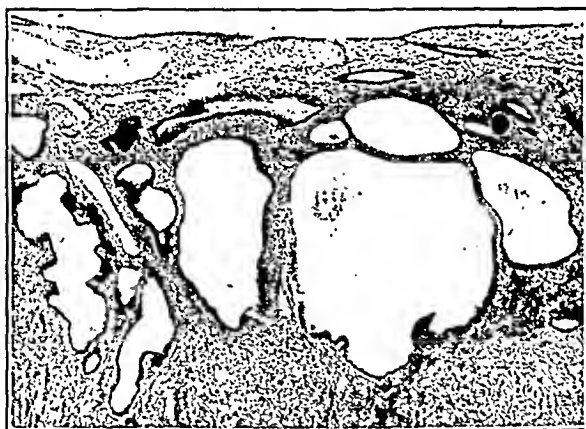


Fig. 7.—(Path. No. 59898.) Low power photomicrograph of uterine endometrium obtained by hysterectomy after administration of 210 mg. of progesterone. There is no evidence of secretory activity.

CASE 7.—The patient, E. W., was first seen in October, 1935, complaining of almost continuous vaginal bleeding for six years. Her menses had begun at the age of 13 years and had occurred every twenty-eight days, lasting five to seven days with no dysmenorrhea, until the age of 18 years, when her menses began to be prolonged. The condition had grown progressively worse until there were only five days during the month in which she was free from bleeding. On physical examination she was found to be a thin, underdeveloped individual with small breasts, showing hair about the areola and male hair distribution abdominally. The clitoris was unusually prominent, but otherwise the pelvic examination was negative. A therapeutic curettage was performed and the diagnosis of endometrial hyperplasia was made.

In August, 1937, she returned to the dispensary with the history of two months' amenorrhea following the curettage, and completely irregular, prolonged, profuse menses since. A forty-eight-hour specimen of urine showed no pregnanediol and an endometrial biopsy showed hyperplasia. She received 2 mg. of progesterone every other day from August 5 to 13, and bleeding which had ceased during the first two days of injections, returned from August 14 to 21. From September 8 to 20 she received 2.5 mg. of progesterone daily. Bleeding occurred September 17 to 21 and was less profuse. On October 7 an endometrial biopsy again showed

(Fig. 5). A second forty-eight-hour specimen collected over the last two days of progesterone injection showed no pregnanediol. The patient ceased bleeding May 27 and had no recurrence until August 4, when she bled again until curettage August 23. Endometrial hyperplasia was again diagnosed.

CASE 5.—F. A., a 12-year-old negress, was seen Feb. 28, 1939, complaining of profuse vaginal bleeding. Her menstrual period had begun December 18 and lasted until January 1. Her next period began January 18 and lasted until February 12 with profuse bleeding. Two days before the dispensary visit vaginal bleeding again recurred. Physical examination revealed a very well-developed child of 12 years with normal pelvic organs. Her basal metabolic rate was minus 13. A suction curettage showed an interval endometrium with a hyperplastic pattern. She received 5 mg. of progesterone daily from March 1 to 10 and a second biopsy showed a typical hyperplasia (Fig. 6). The patient ceased bleeding after the third injection. She had an apparently normal menstruation,



Fig. 5.



Fig. 6.

Fig. 5.—(Path. No. 48553.) Low power photomicrograph of an endometrial biopsy taken after the administration of 50 mg. of progesterone over a ten-day period. There is marked irregularity of the glandular pattern. The gland at the periphery shows marked secretory activity and tortuosity, while the two cross sections of glands show secretory activity of the glandular epithelium but remain dilated as in the previous hyperplastic pattern.

Fig. 6.—(Path. No. 48206.) Low power photomicrograph of an endometrial biopsy taken after 50 mg. of progesterone given in daily doses of 5 mg. There is no evidence of secretion in these glands, which show marked reduplication of the nuclei.

May 11 to 15, immediately following cessation of progesterone. Twenty milligrams of progesterone were given from March 20 to 23 and bleeding occurred from March 25 to 29. Twenty milligrams were again administered April 15 to 18 and bleeding occurred April 21 to 25 normally. When last seen in August, 1939, she had continued to have normal menses.

CASE 6.—This 26-year-old white woman was seen in December, 1937, complaining of constant, profuse vaginal bleeding. Her menses had begun at the age of 16 years and had occurred every twenty-eight days, lasting seven days until her first pregnancy in 1931. Following her delivery, she had amenorrhea for three years which was succeeded by profuse, irregular menses, lasting ten days. In October, 1936, a uterine curettage showed endometrial hyperplasia. She

3. In no case in the present series could a measurable amount of pregnanediol be recovered from the urine before treatment.

4. The amount of progesterone excreted in the urine as pregnanediol, when 50 mg. in 5 mg. doses is given daily, is insufficient to be recovered consistently in measurable quantities in cases of endometrial hyperplasia.

5. Progestational-like changes can be produced in the endometria of hyperplastic cases with doses of progesterone which are too small to be recovered in the urine as pregnanediol by present methods.

6. Progesterone can be recovered in the urine as pregnanediol even though progestational changes do not occur in the endometrium.

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### THE USE OF THE NEUTRAL DIET AND HYDRATION IN THE TREATMENT OF TOXEMIAS OF PREGNANCY

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THE care of toxemic patients has undergone considerable change during the past few decades. Impressed with the work of Newburgh on water balance, we have attempted to utilize his findings in the treatment of toxemias of pregnancy. In order to evaluate the results of our treatment, a study was made of the records of 435 toxemia patients admitted to the University Hospital between the years 1901 and 1938, inclusive. For purposes of comparison the records were divided into two groups, the first including the records of patients admitted between the years 1901 and July, 1931. The second group includes those admitted in the seven-year period from July, 1931 to July, 1938.

The average age for both groups studied is 23 years. The youngest patient was 13 years of age, the oldest, 46 years. The majority were between 20 and 25 years of age, corresponding to the general age group of pregnant individuals.

Primiparas constituted 63 per cent of the entire series. The average parity of the remaining 37 per cent was four. The largest number of pregnancies noted in any one individual was 12, the toxemia occurring first with the seventh child and increasing in severity with each succeeding pregnancy.

With the exception of four colored women, all the patients were white.

The nationality of the patients studied was about the same as a cross section of the population of the state of Michigan in general, mostly American. The remainder were German, Bulgarian, Hungarian, English, and Scandinavian. The latter were represented in extremely small numbers. It is interesting to note that only three patients were of Latin extraction.

The patients were classified according to Stander's classification of toxemias of pregnancy.<sup>1</sup> While we do not subscribe to this classification in its entirety, it is well known and widely used. The incidence of the various toxemias is shown in Table I. The so-called pre-eclamptic form predominated in both groups. Nephritic

hyperplasia. Five milligrams of progesterone a day were given for six days and a specimen of urine taken over the last two days of administration demonstrated a trace of a crystalline substance which was assumed to be pregnanediol, but was too small an amount to verify with a melting point. A suction curettage at the end of treatment again showed hyperplasia. Three days after cessation of progesterone, the patient bled for eight days. On December 14, ten days before the next expected menstrual period, she again received 5 mg. of progesterone over a ten-day period. A curettage before therapy had again shown hyperplasia, but unfortunately after therapy an insufficient amount of tissue was obtained for a satisfactory microscopic study. Two days after discontinuation of progesterone the patient had an apparently normal five-day menstrual period. The same plan of treatment was carried out during the month of January; at this time an endometrial biopsy was obtained after 50 mg. of progesterone had been injected, which showed secretory changes. The patient again had an apparently normal menstrual period two days after her last injection was received. The following month the progesterone was reduced to 20 mg. in all and she again bled two days after withdrawal. No progesterone was given in March, and the patient had only scanty bleeding one day. March 23, and again on April 26. Menses lasted seven days and were profuse in June and July. She missed her August period and bled from September 24 to 30. On October 9 she again began to bleed and continued until November 28, when a biopsy showed a recurrence of endometrial hyperplasia. Forty-eight-hour urine specimens collected on November 12 and 13 and again November 19 and 20 showed no pregnanediol, and 30 and 14 rat units of estrogen per 24 hours, respectively. From November 28 to December 7 she received 5 mg. of progesterone daily. Bleeding stopped on November 30. A curettage on December 8 showed secretory changes in the endometrium, and a specimen collected on December 6 and 7 showed 0.7 mg. of pregnanediol with a melting point of  $220^{\circ}$  to  $230^{\circ}$ . There were 50 rat units of estrogen per 24 hours. Bleeding occurred from December 10 to 15. The subsequent course of treatment is recorded in Table I.

TABLE I

PROGESTERONE TREATMENT	BLEEDING DATE	ESTROGEN PER 24 HOURS	PREGNANEDIOL
—	—	116 Rat units	0—Dec. 26 and 27
50 mg. Dec. 28 to Jan. 7	Jan. 9-13	28 Rat units	0—Jan. 6 and 7
—	—	25 Rat units	0—Jan. 29 and 30
20 mg. Jan. 31 to Feb. 3	Feb. 5-10	16 Rat units	0—Feb. 2 and 3
—	—	—	0—Feb. 27 and 28 0—
20 mg. Feb. 28 to March 3	March 11-13	—	0—March 2 and 3
None	April 7-12	—	—
None	May 16	—	—

## CONCLUSIONS

1. Endometrial hyperplasia may respond to progesterone and show changes resembling the physiologic response.
2. Three of seven cases of hyperplastic endometria did not respond to progesterone. Either 50 mg. of progesterone over a ten-day period is an insufficient dose or some cases are refractory to the hormonal influence.

a neutral or slightly acid ash. The food is prepared and served without salt. Bread is made without salt and sweet butter is used. The average diet contains between 70 and 85 gm. of protein.

Ammonium chloride is used to release the sodium ion from the tissues. It is given in gelatin capsules with the meals in doses from 8 to 12 gm. daily; when it is absorbed from the gastrointestinal tract, it is carried to the liver and there broken down to form urea. From there on, ammonium chloride is circulating in the blood stream in the form of urea and the chloride ion. The urea is excreted as such. The chloride ion, when it reaches the tissues, conjugates with the sodium from the sodium acid carbonate,  $\text{NaH}_2\text{CO}_3$ , and the sodium is excreted as sodium chloride. With the prolonged use of ammonium chloride, the kidney has a tendency to convert the urea back into ammonium ion, and consequently the ammonium is excreted as ammonium chloride, and the sodium ion continues to be retained by the tissues. For this reason, ammonium chloride is given for not longer than a period of three to four days at a time. With the elimination of sodium, edema fluid, which is retained by the sodium ion, is also given up. At the same time the intake of sodium is decreased by the neutral diet, which has a decreased amount of available base.



Fig. 1.

Fluids are forced, 4,000 to 5,000 c.c. being administered daily to insure a urinary output of from 2,500 to 3,000 c.c.

There are three advantages to this method of therapy: the free excretion of waste material and solids in water, the maintenance of normal water balance, and a decreased amount of available sodium. The neutral diet is also used in severe pre-eclamptic toxemias. Toxemic patients in coma are not fed for a period of three days to induce a mild acidosis. With this acidosis, diacetic acid produces the same effect as ammonium chloride in the other group by combining with the sodium ion and excreting it in the form of sodium diacetic acid. Fluids are given intravenously in large amounts to combat any element of uremia that may be present; we feel that the risk associated with forcing fluids is not very great, because the amount of rise in blood pressure is not of a significant degree. Also we do not feel that there is a risk of increasing cerebral edema if 5 per cent glucose solution is used, but do feel that there is a real risk of increasing intercellular fluids and retention of electrolytes if saline is used. If patients respond to this form of therapy, they are later placed on adequate neutral dietary intake, including ammonium chloride.

TABLE I. COMPARISON OF PER CENT OF 2 GROUPS

TYPES	GROUP I (1901-31)		GROUP II (1931-38)		TOTAL	
	NO.	%	NO.	%	NO.	%
Low reserve	36	15.0	13	7	49	11.0
Nephritic	43	18.0	18	9	61	14.0
Pre-eclamptic	74	31.0	128	66	202	46.5
Eclamptic	35	14.5	20	10	55	12.5
Unclassified	53	22.0	15	8	68	15.5
Total	241	100.0	194	100	435	100.0

toxemia of pregnancy was second and eclampsia was third. These groupings were based on available clinical and laboratory data found in the patients' records. The relatively higher incidence of toxemias in Group II, from 1931 to 1938, was probably due to the development of more satisfactory investigative methods, and more complete recording of resulting data, and probably does not therefore represent an increase in incidence alone. There were 5,076 deliveries between 1901 and 1931, of which 241 were toxemic, an incidence of 4.7 per cent. In Group II there were 3,193 deliveries, of which 194 were toxic, an incidence of 6 per cent. This makes a total of 435 toxemias in 8,269 deliveries over the entire period studied, an incidence of 5.4 per cent for the entire period.

#### TREATMENT

For the patients in Group I, 1901 to 1931, treatment consisted in the main of: (1) general care with a short period of observation, (2) special measures, usually operative, for the termination of pregnancy. Most of the patients seen during this period were admitted in urgent need of treatment. Because of this, treatment usually resolved itself into a matter of determining the most satisfactory method of terminating pregnancy for that particular individual.

In keeping with the trend of the time, many of the patients seen during the period covered by Group I were, upon admittance, first placed on the then popular low-protein, salt-free diet. If this failed to control the toxemia symptoms, some means of terminating the pregnancy was carried out. The incidence of terminating pregnancy by cesarean section during the period covered by the first group was quite high and reached its peak, 11 per cent, in the years 1912 to 1916. As noted in Fig. 1, the incidence of cesarean section and induction of labor follow an inverse ratio.

That therapy in Group II was markedly conservative is shown by the reduced incidence of cesarean section, 2.6 per cent. Treatment during this second period was characterized by specific remedial measures, to be mentioned later, directed toward the control of the toxemia, and by induction of labor, usually by rupturing the membranes.

Therapy in Group II, 1931 to 1938, was first along the lines suggested by Arnold and Fay<sup>2</sup> and now commonly known as the Temple or dehydration method of treatment. Twelve patients were treated by this method, too small a number to warrant drawing any conclusion. One death occurred in the group treated by this method.

During the past six years, hydration has again dominated our medical management of these patients. In the presence of a significant toxemia, hospitalization, bed rest, sedation, neutral diet, ammonium chloride, and abundant fluids form the basis for our therapy.

One hundred and fifty-two patients in Group II were treated by this method. The neutral diet is the type suggested by Newburgh and Lashmet<sup>3</sup> consisting of foods which yield equal amounts of acid and basic ash to which are added foods which yield a neutral ash, such as butter, sugar, and tapioca. The diet is not strictly neutral, but somewhat on the acid side, a desirable feature in patients with edema. The diet is further characterized by its low sodium content and



TABLE II. MORTALITY, TOXEMIA WITH CONVULSIONS

	GROUP I (1901-31) 35 CASES		GROUP II (1931-38) 20 CASES		TOTAL (1901-38) 55 CASES	
	NO.	%	NO.	%	NO.	%
Maternal mortality	7	20	2	10	9	16
Fetal mortality	17	50	5	25	22	40

Twenty patients with eclampsia were treated during the past seven years, with a mortality rate of 10 per cent, or one-half that recorded for Group I casts. Of these, 16 patients were treated by neutral diet, hydration, and sedation only.

## SUMMARY

1. Patients with toxemias of pregnancy admitted to the University Hospital are generally managed conservatively.

2. Toxemias of pregnancy are treated by what we call the hydration method, consisting of abundant fluids, neutral diet, ammonium chloride, bed rest, and mild sedation.

3. If, and when, this conservative regime fails to control the toxemia, termination of pregnancy by the most conservative means suited to the particular individual is carried out.

4. During the period 1931 to 1938, the maternal mortality rate has dropped to 2.6 per cent, the fetal mortality rate to 16.4 per cent, which is approximately one-half the death rate for patients treated during the years 1901 to 1931.

5. There has been one maternal death in the group of 152 toxemias of pregnancy treated by the hydration method since 1933.

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Boycott, Muriel, and Smiles, J. M.: Diagnosis of Hydatidiform Mole by Biological Assay, Lancet 1: 1428, 1939.

The authors report a case in which hydatidiform mole was suspected and in which a 1 in 200 dilution of the urine gave a positive Friedman test. Subsequent evidence, including microscopic examination of the placenta, failed to confirm the diagnosis. They point out that the excretion of gonadotropic hormone in normal pregnancy may reach a higher level than is usually recognized. The maximal excretion occurs at about the stage of normal pregnancy (eight to twelve weeks) when the presence of hydatidiform mole is likely to be suspected. This excretion is increased in cases of pernicious vomiting. Although in most instances of hydatidiform mole and chorionepithelioma there is a larger excretion of gonadotropic hormone than in any other condition, there is such a range of excretion values that the diagnosis of hydatidiform mole on such assay alone is unreliable.

CARL P. HUBER.

In considering the entire group of patients over both periods of study, it will be seen that the trend toward conservatism continues. Diet and fluid therapy are actively used to combat edema, which is thought to be a factor in the aggravation of toxemia.

### MORTALITY

As noted in Fig. 2, the highest maternal mortality rate was coincident with the high rate of cesarean section. The evaluation of cesarean section as a means of terminating pregnancy or as a means of treatment on the basis of our data, is likely to be misleading. We have no desire to debate the question of cesarean section as a means of treatment for severe toxemia of pregnancy, but do wish to point out that the high mortality noted during the time when cesarean section was frequently used, 1912 to 1916, might, in part, be attributed to the undeveloped technique of the operation. In the first group, from 1901 to 1931, the maternal mortality rate for all patients was 7 per cent. The fetal mortality was 30 per cent. It is also to be noted that our fetal mortality rate reached its peak at the same time that the maternal mortality rate and the cesarean section rate were highest.

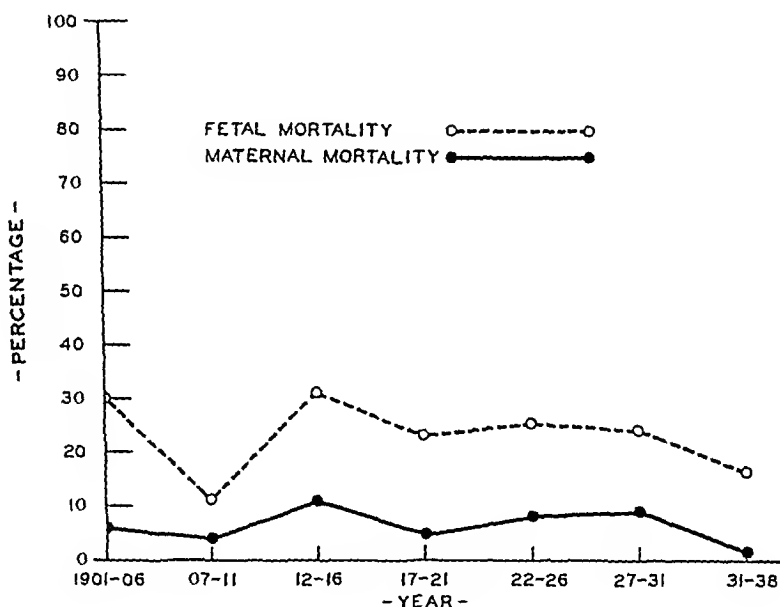


Fig. 2.

The maternal mortality rate for all Group II cases, 1931 to 1938, was 2.6 per cent, with a fetal death rate of 16.4 per cent. Of the maternal deaths in this period, four were directly the result of the toxemia, one occurring shortly after admittance in a patient having convulsions. One maternal death was the result of postoperative shock. Only one occurred in a patient who had been treated by the so-called hydration method, occurring ten hours post partum. The maternal mortality rate from toxemias of pregnancy in this clinic is lower at the present time than at any other time during the thirty-seven years covered by this study.

### ECLAMPSIA

There were 55 cases of toxemia of pregnancy with convulsions. Of these, 28 patients were having convulsions at the time of admittance or developed convulsions within twenty-four hours. The remaining 27 developed eclampsia after having been in the hospital more than twenty-four hours.

The maternal and fetal mortality rates for both groups are recorded in Table II.

Cesarean section was resorted to in 13 of the 55 cases, but only one of these was performed during the last seven years.

four years we have observed 5 cases in which a diagnosis of gonococccic perihepatitis was made. All of them had salpingitis following an acute gonococcal infection of the urethra or cervix or both. We found that tubal extensions are at times delayed as long as ninety days after the disease is contracted. The number of women who have a pelvic extension is large. In our clinic, considering all admissions,<sup>10</sup> upwards of 30 per cent have a tubal involvement.

#### CASE REPORTS

CASE 1.—(W-39512.) A white unmarried woman, aged 24 years, occupation: waitress, was admitted to the Institute Sept. 10, 1936, with a vaginal discharge and lower abdominal pain which had been present at intervals since receiving treatment for gonorrhea two years ago. She was accused of transmitting the infection ten days prior to our examination. She admitted being treated for gonorrhea two years ago and was discharged after a few weeks following one negative slide. She was exposed ten days prior to our examination.

General physical examination was negative. There was a profuse purulent discharge from the vagina. The urethra was inflamed and Skene's glands were thickened. There was no pain or tenderness on bimanual examination. Gonococci were found in the cervical slide. This was an acute infection. She received local treatment for several visits and a few days before her menses she complained of pain in the lower abdomen and thighs. Bimanual examination disclosed tenderness over the adnexa, but no masses were palpable. All local treatment was discontinued, and she was advised to stay in bed and use hot applications. On her visits to the clinic, intramuscular injections of foreign proteid at forty-eight to ninety-six hour intervals were given. After receiving the fifth injection she complained of pain in the right upper quadrant on respiration, and she was tender on palpation. Auscultation was negative. The symptoms were suggestive of cholecystitis but quite atypical. Her temperature was 99° F. and it never went above 100°. Complete rest in bed and heat locally was the treatment which she had at home. Within four days she was free from pain and was out of bed within a week. The patient continued under our care following this complication, and she was pronounced bacteria free after three months' treatment. She was examined one year later and both tubes were found to be slightly thickened and the fundus was posterior and limited in motion.

CASE 2.—(W-46601.) A white, divorced woman, aged 20, occupation: waitress, was admitted to the Institute Feb. 18, 1939, with vaginal discharge, urgency, urinary frequency and painful urination, and pain in both lower quadrants. Her symptoms had been present for two weeks. She has also had metrorrhagia and rectal bleeding at intervals for several months. She has never received treatment for gonorrhea. She had an appendectomy and a right salpingectomy in 1934 and a left salpingectomy in 1937. She admitted numerous contacts while working in a tavern. The general physical survey showed no pertinent pathology. There was tenderness over the lower abdomen on palpation. The pelvic examination disclosed an eroded cervix, and there was a bloody purulent discharge in the fornix. A tender mass the size of an orange was found in the left adnexa. A rectal examination revealed large internal hemorrhoids. The slides from the urethra showed many typical intracellular diplococci. She was given foreign proteid in moderate size doses and 40 gr. each of sulfanilamide and soda bicarbonate, and advised to stay in bed and use any form of heat to her abdomen. She reported in four days and was still suffering pains in the lower abdomen. At this visit her temperature was 99° F. Her next visit was in forty-eight hours and she was greatly improved. The injections of foreign proteid were continued. The patient was out of the city for one week and upon her return she stated that after riding in a bus for ten hours she had an attack of pain in the right upper quadrant which was greatly increased upon deep inspiration and motion. The attack was sub-

# ACUTE GONOCOCCAL PERIHEPATITIS

## WITH REPORT OF FIVE CASES

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GONOCOCCAL perihepatitis as a pathologic entity was first accurately described by Curtis<sup>1</sup> in 1930. He reported the frequent occurrence of multiple bands of adhesions, which were defined as resembling "violin strings," between the anterior surface of the liver and the parietal peritoneum in female patients coming to operation who had a chronic gonococcal infection of the tubes.

In a later contribution Curtis<sup>2</sup> reported 24 patients upon whom he had operated and found these perihepatic adhesions, and all of them had a residual specific infection of the adnexa. These stringlike adhesions are found to extend over a wide area on the anterior surface of the liver and the anterior abdominal wall, but fortunately they are of sufficient length to permit free movement between the viscus and the muscular wall during respiration. Fitz-Hugh<sup>3</sup> in 1934 reported 3 cases of acute right upper abdominal pain associated with acute gonococcal salpingitis. One of his patients had a laparotomy during an attack, a presumptive diagnosis of acute cholecystitis being made. But when the abdomen was opened, an acute peritonitis was found involving "the anterior surface and edge of the liver and the abdominal wall." He crisply described the pathology in the following manner: "The peritoneum in these areas was injected and had the appearance of salt sprinkled on a moist surface." He further commented to the effect that "from the drainage tract in this case typical gram-negative intracellular diplococci were later recovered." The patient upon being told that gonococci were found in the wound admitted having a gonococcal infection with an accompanying salpingitis and bacteriemia some years previously. This internist and his surgical consultant reached the conclusion that what they had observed at the operation was the acute stage of gonococcal perihepatitis, the process described in its chronic form by Curtis.

Hinton<sup>4</sup> has reported his observations on adhesions in right upper abdominal pain, also Lyon<sup>5</sup> and Ellison<sup>6</sup> have discussed the causes of residual pathology in this region. Scott<sup>7</sup> has written on this subject and reported a case with a sub-diaphragmatic abscess of gonococcal origin. Bearse<sup>8</sup> reported an interesting case in which the patient was operated upon for a presumable highly placed appendix during an acute attack, but examination of the abdominal organs revealed the presence of many cobweb and unorganized fresh adhesions between the liver and the anterior abdominal wall.

Recently Hertz<sup>9</sup> of the Mayo Foundation reported an interesting case of severe right upper quadrant pain which was suggestive of acute cholecystitis, but slides and cultures from the genitalia showed typical gonococci. A bilateral adnexitis was discovered. The patient received conservative treatment with hot baths, an erythema dose of x-ray and hyperpyrexia, and all symptoms were relieved, and she was rendered bacteria free promptly and returned to work one week after receiving fever therapy. This writer also discussed at length the clinical picture, pathology, differential diagnosis, and treatment of gonococcal perihepatitis.

In our clinic for women we discover and treat several hundred female patients presenting gonococcal infections annually. In the past

upper abdomen. There was pain upon deep breathing and coughing. There was a slight elevation of temperature, 99.8° F. Examination of her chest was negative, but there was great pain on pressure over the costal margin. Hospitalization was advised and she consented and was admitted to the hospital. She remained in the hospital for five days and was improved, and against the advice of the attending physician she went home. Her condition remained stationary for several weeks, but at the end of the eighteenth week of treatment, she was in excellent condition. After her stormy and long-continued disability, she confessed to dancing, sexual excitement, and the use of alcohol. This patient was under treatment and observation for eight months. She was re-examined three months after being discharged, and there were no pelvic or hepatic residuals discoverable.

CASE 5.—(W-46555.) A white woman, single, aged 27 years, unemployed, was referred on Feb. 11, 1938, by her sexual partner who was under treatment for gonorrhea. She had noticed a vaginal discharge and pain and burning on urination for a week prior to admission. She had an uncomplicated gonococcal infection five years ago which was contracted from the same contact. There was no history of any confining illness or operations.

Our general physical survey was negative. Vaginal examination disclosed an acute urethritis, a profuse purulent vaginal discharge, and an erosion of the cervix. The right tube was slightly enlarged and tender. Slides from the urethra, cervix, and rectum all showed typical intracellular gonococci. She was placed on treatment, and topical applications were made to the urethra and cervix. Sulfanilamide and soda bicarbonate, 40 gr. daily, were prescribed. She returned within forty-eight hours complaining of pains in the lower abdomen, especially on the right side. Her menstrual period was not due for two weeks. At this visit her temperature was 99° F. and pulse 90, and the physical findings were negative. She was instructed to return home and stay in bed, and should her condition become worse she was to notify us. The patient left the city and her physician notified us that she was quite ill with severe pains in the right upper quadrant of the abdomen which resembled an "acute cholecystitis." He administered neoprontosil daily subcutaneously and gave her 60 gr. of prontosil by mouth every twenty-four hours and applied ice bags. The patient remained in bed for three weeks but her symptoms had disappeared after the first week's confinement. Local treatment was instituted after she was ambulant. She was dismissed as cured May 15, 1939, after being under treatment and observation for ten weeks. We made several physical examinations and a number of slides, and all of them were negative before she was dismissed from treatment.

#### DISCUSSION

There is no doubt that perihepatitis as a complication of pelvic inflammatory disease is much more common than the reported cases in the literature would lead physicians to believe. There can be little question that missed and wrong diagnoses of this condition are not uncommon, and especially is this true when a careful gynecologic examination and bacterial study of cervical and urethral secretions are omitted.

The question is often asked, "How does the infecting organism reach the liver?" We agree with the clinicians who have suggested that the gonococci reach the anterior surface of the liver by way of the lymphatics or blood stream. Pathologists have not yet reached satisfactory conclusions concerning the spread of the infection or which of these routes is the most common. Curtis has seen several cases where there has been an ascending infection along the colon, also inflammation ascending "the paravertebral gutter," and so perhaps some of these cases are ascribable to contiguity.

siding when the patient next reported but she complained of tenderness on pressure over the liver area. Her temperature was normal at this time. We did not see the patient again for three weeks and at this visit, March 20, she was symptom free, but there was tenderness on palpation over the right costal margin. Local treatment was administered on April 5 and continued very irregularly for four weeks and at her visit on May 8 she was bacteria free. She failed to return for further observation. This patient had a mild attack of perihepatitis from which she rather promptly recovered.

CASE 3.—(W-39555.) A white married woman, aged 28 years, occupation: office clerk, was admitted to the Institute Sept. 15, 1936. Her complaints were vaginal irritation and discharge for five weeks. There was no history of any severe illness. She has been separated from her husband for eighteen months but admitted having sexual relations with him. The state of his health was unknown.

Examination disclosed an undernourished white female in poor physical condition. Teeth were carious, mouth foul, cervical and inguinal glands enlarged. The abdominal wall was relaxed and a small umbilical hernia was present. The vaginal examination disclosed an acute urethritis with profuse purulent vaginal discharge and an hypertrophy of the cervix which was lacerated and chronically inflamed. Fundus was anterior and normal. Adnexa were negative. Slides from the cervix showed many typical intracellular gonococci. Cervical slides were later found to be positive. The patient made good progress under treatment but at the first menstrual period, two weeks after admission, she had slight discomfort in the lower abdomen. The physical findings at this time were negative. For eight weeks her condition was satisfactory but at the third menstrual period, about twelve weeks after admission, she complained of severe pain in the lower abdomen without nausea or vomiting. Within forty-eight hours after the pain began in the lower abdomen, she reported to the clinic and complained of severe sharp pain on respiration in the right upper quadrant. Her temperature was normal. There was pain on deep palpation over the margin of the liver. Auscultation was negative. Hospitalization was advised but the patient refused as she could not afford the expense. She remained in bed at home and used hot applications to the right chest. She was comfortable while recumbent, and on her visits to the Institute, she received intramuscular injections of foreign proteids. She made a complete recovery and was symptom free within ten days. She was discharged from treatment and observation eight weeks after her acute attack. She was under observation for three months following the complication, and she was in excellent condition when last seen.

CASE 4.—(W-44615.) A white woman, single, aged 18 years, unemployed, was admitted to the Institute Aug. 8, 1938. She gave a history of an acute gonococcal infection twelve months ago and had received treatment until eight weeks before admission. She has had a persistent vaginal discharge for months, with irritation of the vulva, frequency and urgency of urination. She admitted sexual exposure one week before admission.

Our general examination was wholly negative. Vaginal examination disclosed a profuse purulent urethral and vaginal discharge. The uterus and adnexa were normal. The urethral and cervical discharge revealed many intracellular diplococci. A diagnosis of gonococcal urethritis and cervicitis was made and the patient placed on treatment. Her condition was excellent until her menstrual period which occurred four weeks after she was admitted. At her visit on September 8 she complained of pains throughout the lower abdomen. She was tender to palpation but there were no signs of rigidity. Bimanual examination disclosed tenderness over both adnexa, and the right tube was enlarged. There was no temperature or nausea or vomiting. The patient was receiving 40 gr. of sulfanilamide and soda bicarbonate daily. On her visits to the Institute foreign proteid was administered. With rest in bed and hot applications, the abdominal pain was relieved and she went back to work. At her second menstrual period, within eight weeks, she suffered two attacks of pain, but they subsided under conservative treatment. At her visit on Oct. 19, 1938, she complained of excruciating pain and tenderness over the right

is positive, the rabbit injected with 0.025 c.c. is opened. If this test is negative, further injections in smaller dilutions were made on additional test animals, i.e., 0.05 c.c.; 0.1 c.c., etc. On the other hand, if the 0.025 c.c. test is positive, higher dilutions are injected, i.e., 0.0125 c.c.; 0.00625 c.c., etc. We thus eventually get two fractional tests, one of which is positive and the other negative. The smallest fraction giving the positive reaction is considered the minimal positive test. Dilutions are made with tap water. Care must be taken that all test animals meet the requirements previously mentioned. Three or four animals are usually required for each quantitative test. Since we laparotomize the rabbits and use them in the future (an animal can be used on an average of four or five times), the test does not involve too much expense. Furthermore, any laboratory capable of performing clinical Friedman tests should be in a position to perform the fractional test.

#### HYDATIDIFORM MOLE

The fractional Friedman test findings in seven cases of hydatidiform mole are tabulated in Table I. It will be noted that in three of these cases (Mole 2, 4, and 7), positive tests were obtained with high dilutions, namely 0.00625 c.c., confirming the usual impression of a high concentration of gonadotropic hormone in the urine of these patients. Likewise in Mole 5, the positive test with 0.025 ( $\frac{1}{40}$ ) c.c. is well above the standards of normal pregnancy for that particular period of pregnancy. However, study of the table will reveal that in Moles 1 and 6, more urine was required to produce a positive test, than the average for this stage of normal pregnancy, and in Mole 3, the contrast is not particularly striking, since the amount needed for this positive test was identical with the highest dilution test for normal pregnancy in that particular week.

Study reveals that those cases positive in high dilutions showed, on pathologic examination, a typical vesicular mole. In contrast Moles 1 and 3 were of the "fleshy" type and contained comparatively few vesicles. In Mole 6, the pathology was typical of the vesicular type, however, the specimen of urine was obtained the same day that the mole was expelled.

It is our impression that high dilution tests will be obtained only if one is dealing with an active vesicular type of mole. If the mole is of the fleshy type, or has, perhaps, ceased to grow, or is actually undergoing degeneration, we may not obtain positive reactions with high dilution tests.

#### CHORIONEPTHELIOMA

From a diagnostic viewpoint, the ordinary qualitative Friedman or Aschheim-Zondek test will suffice when chorioneptelioma is suspected. On the other hand, the quantitative test may be of value as a prognostic aid. We present the fractional Friedman tests on three patients with chorioneptelioma in the lower part of Table I. All of these cases terminated fatally.

It will be noted that two of these cases followed hydatidiform moles. This, of course, is generally understood, but it should serve to point out the necessity of carefully watching any patient who has had a hydatidiform mole. Such patients should have monthly Friedman or Aschheim-Zondek tests for at least one year after the expulsion of the mole. While it is true that these patients may have positive tests for a matter of weeks or possibly two months after the mole is expelled without actually having a chorioneptelioma, the positive test cannot be disregarded. Here the quantitative test will be of value. In the event of repeated positive qualitative tests, or positive high dilution tests, the patient is certainly entitled to a diagnostic curettage. It is generally conceded that a positive test is of diagnostic value in suspected chorioneptelioma and may be the first indication of such pathology.

#### DIFFERENTIAL DIAGNOSIS

We have found that other conditions associated with pregnancy may give high-dilution positive tests. While we have never obtained a positive test in normal uncomplicated pregnancy with amounts smaller than 0.05 ( $\frac{1}{20}$ ) c.c., we have found that pregnancy complicated by hyperemesis gravidarum shows an excessive amount

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## DIAGNOSTIC FRIEDMAN TEST IN HYDATIDIFORM MOLE AND CHORIONEPITHELIOMA\*

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IT IS generally understood that the urine of patients with hydatidiform mole contains an excessive amount of the gonadotropic hormone, which is responsible for the reaction obtained in the Aschheim-Zondek and Friedman tests. With this thought in mind, we have attempted to determine the minimum amounts of urine, at the various stages of normal intrauterine pregnancies, which will give positive Friedman tests. The establishment of such normal standards provides the basis for a quantitative Friedman test.

We are expressing these standards in terms of actual amounts of urine required. Most quantitative hormonal studies report results in units per given amount of urine. However, the hormonal units do not seem to be generally agreed upon. In order to keep this quantitative test practical and avoid confusion, no attempt has been made to express results in units.

### METHODS

We obtained our standards by intravenously injecting fractional amounts of urine in test animals of certain specifications. The animals used were virgin female rabbits, between the ages of 3.5 and 4.5 months and weighing at least 1,500 gm. The urine was injected in fractions as follows: 0.0125 ( $\frac{1}{80}$ ) c.c.; 0.025 ( $\frac{1}{40}$ ) c.c.; 0.05 ( $\frac{1}{20}$ ) c.c.; 0.1 ( $\frac{1}{10}$ ) c.c.; 0.5 ( $\frac{1}{2}$ ) c.c.; 1.0 c.c.; 3.0 c.c.; and 5.0 c.c.

These standards, based on quantitative studies on 149 pregnant patients, are shown in the upper part of Table I. The lowest and highest dilution tests for the given weeks of pregnancy are tabulated. The average minimal amounts of urine necessary to produce positive tests are shown for the various weeks of pregnancy.

### TECHNIQUE OF FRACTIONAL TEST

When a urine specimen is submitted from a suspected case of hydatidiform mole, a qualitative test is started, i.e., 15 c.c. of urine is injected in the marginal ear vein of a test rabbit in two doses of 7.5 c.c. each at intervals of twenty-four hours. The animal is laparotomized forty-eight hours after the first injection and the test read. At the same time the qualitative test is started, another animal is injected with 0.025 c.c. of the urine. If the qualitative test is negative, it is obvious that the fractional test will give no further information. However, if the clinical test

\*Aided by a grant from the Hendricks Research Fund.



of gonadotropic substance in the urine. Five cases of hyperemesis were positive with 0.025 c.c. and two positive with 0.0125 c.c. All of these tests were confined to the interval between the seventh and twelfth weeks of pregnancy.

Likewise we have obtained high-dilution positive tests in multiple pregnancy. Thus, in two cases of twins studied, one was positive with 0.0125 c.c. and the other with 0.00625 c.c. A case of triplets was positive with 0.025 c.c.

With these findings in mind, it can be seen that care must be exercised in the interpretation of high-dilution positive tests. Thus, one could visualize a case of multiple pregnancy associated with hyperemesis gravidarum and complicated by a threatened abortion. Both clinical and laboratory findings might very well simulate hydatidiform mole. One sees the importance of the differential diagnosis, when we consider the contrasting treatments of these simulated possibilities.

#### SUMMARY

We have presented the technique of a fractional Friedman test, which can be carried out in any laboratory capable of performing clinical Friedman tests. The average minimal amounts of urine necessary to produce positive reactions in the various weeks of pregnancy are given. These findings form the basis of the quantitative Friedman tests.

Results of the quantitative tests of 7 cases of hydatidiform mole and 3 cases of chorionepithelioma are reported. While 4 of the patients with mole showed evidence of excessive gonadotropic hormone in the urine, the other 3 patients did not. Thus we may not rely entirely on this finding in all types of hydatidiform mole. Two patients with chorionepithelioma showed the gonadotropic hormone present in considerable concentration. It is felt that the ordinary qualitative test will suffice for diagnosis in chorionepithelioma, but that the quantitative test will often prove of value in this condition.

Since 2 of the 3 chorionepitheliomas developed consequent to the expulsion of hydatidiform moles, the necessity of following postmole cases with monthly Friedman tests for a period of at least one year is emphasized.

It is further pointed out that certain complications of pregnancy, namely hyperemesis gravidarum and multiple pregnancy, may also show an excess of the gonadotropic hormone in the urine. Hence, these conditions must be kept in mind in making differential diagnoses.

These findings of gonadotropic substance in the urine have been confirmed by quantitative studies on blood serum. These latter are not included, since it is felt that the urinary determinations will suffice for clinical application.

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Kubota, T.: A Case of Fetal Death Due to Small Dose of Quinine, *Jap. J. Obst. & Gynec.* 22: 128, 1939.

Quinine has long been used to stimulate uterine contractions. However, a few cases have been reported in the literature where quinine was responsible for the death of a baby. Kubota adds a case to this group. The total amount of quinine given to the mother was 0.29 Gm. (almost 4 gr.). The author believes that the baby died because it was sensitive to quinine. He urges caution in the use of this drug for the purpose of stimulating uterine pains at the end of pregnancy.

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The patient was admitted for observation, and on January 6, at 5 P.M., labor began with five- to seven-minute pains of fair duration. By 2 A.M. January 7, the cervix was 3 fingers dilated and the presenting part was at the level of the spines. Analgesia was obtained with sodium amytal and scopolamine, and at 6 A.M. the cervix was fully dilated. The presenting part was below the spines and the fetal heart was good. Two and one-half hours later, despite good pains, the patient still had not delivered. Vaginal examination revealed the head in the midpelvis in R.O.T. with considerable caput formation and molding. The cervix was completely dilated. Because of the prolonged second stage, abnormal position, and small midpelvis and outlet, Barton forceps were applied in the transverse and, after episiotomy and considerable traction, the patient was delivered of an apparently healthy male child, weighing 7 pounds 6½ ounces. The third stage required three minutes and no excessive bleeding occurred. The episiotomy was repaired and the patient was returned to bed in good condition.

On the first post-partum day, although the patient was comfortable, the temperature rose to 101° F. On the second day it rose to 102.2° F. and marked abdominal distention was noted. No tenderness was present. The patient had had no chill. Milk and molasses enema, Harris drip, and pitressin were effective in reducing the distention somewhat. A vaginal culture showed gram-negative bacilli. On the third post-partum day the temperature rose to 103.6° F., pulse to 130, distention again became marked, and inability to void was notable. The next day the temperature fell to 102° F. while the pulse remained at 140. During all this time the patient looked surprisingly well and offered no particular complaints. Lochia was not foul, distention persisted, urinalysis was negative, and the white blood count showed 17,000 cells with 74 per cent polymorphonuclear neutrophils. It was believed that the patient was suffering from a syndrome closely resembling paralytic ileus and she was transferred to the isolation ward at this time. On the fifth post-partum day the temperature reached 104° F. and a blood culture was taken. This was reported later as showing staphylococci. The urine was normal. On the sixth and seventh days, the temperature continuing high, aerobic and anaerobic blood cultures were taken and, after incubation, gram-positive spore-forming bacilli were noted in pure culture in both media.

During the entire post-partum period, the patient had had only one slight chill. On the eighth day the temperature was 103.4° F. and complete examination was undertaken. The breasts were normal; the abdomen was slightly distended and soft. The uterus, at the level of the umbilicus, was firm and a little tender. The lochia was scant, brown, and not foul. Vaginal examination revealed the cervix to be soft and a finger tip dilated. The uterus was soft and not tender. No parametrial pathology could be made out. It was thought most likely at this time that the patient was suffering from a localized intrauterine infection. The red blood count was 4.3 M; Hg, 65 per cent; white blood count, 24,300 with 86 per cent polymorphonuclear neutrophils. Stool cultures were negative for typhoid, paratyphoid A and B, and dysentery. On the ninth day a transfusion was started, but after 75 c.c. of blood had entered the vein, the patient complained of abdominal cramps and experienced a chill. The transfusion was discontinued immediately and 0.5 c.c. each of Magendies' solution and adrenalin was given. The temperature quickly rose to 106.4° F. There was no cyanosis and no respiratory distress. The pulse, however, rose to 150. After the intravenous administration of 2,000 c.c. of 5 per cent glucose in saline, the temperature began to fall and the reaction appeared to be over. Urinary output remained good and no hemoglobinuria was noted. On the tenth day, aerobic and anaerobic blood and uterine cultures were taken and in all a gram-positive, spore-forming bacillus was noted in pure culture. This organism was in all respects similar to that observed on the cultures taken on the sixth day. The temperature continued rising to 104° F. for the next three days, and on the thirteenth day a slow transfusion of 500 c.c. of citrated blood was given without apparent reaction. Urine culture taken at this time revealed *B. coli*, staphylococci and fusiform bacilli. On the fourteenth day, the temperature again rose precipitously to 104.2° F. and the patient complained of a sharp, stabbing pain in the right upper chest accompanied by a distressing nonproductive cough. Backache radiating to the groin was also noted. Examination revealed diminished

## PARAMETRIAL ABSCESS AND PUERPERAL SEPTICEMIA DUE TO AN UNUSUAL ORGANISM\*

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**I**NFECTION with aerobic spore-forming motile bacilli has been reported in the literature but is sufficiently unusual to be interesting. The pathogenicity of many of the reported organisms has been limited to experimental animals, but Bais,<sup>1</sup> Charrin and De Nittis,<sup>2</sup> Kelemen,<sup>3</sup> Legros and Lecène,<sup>4</sup> Lindberg,<sup>5</sup> Senge,<sup>6</sup> Stregulina<sup>7</sup> and Sweany and Pinner<sup>8</sup> have reported various human infections with organisms of this group. Most of these authors described the organism as "pathogenic subtilis" and some used the term *Bacillus anthracoides*. In 1935 Siribaed<sup>9</sup> in Siam described a pathogenic variety of aerobic spore-forming bacillus, the origin of which he does not suggest, but which he called *Bacillus siamensis*. He believed it to be a pathogenic variety of *Bacillus subtilis*. Clark<sup>10</sup> in 1937 reviewed Siribaed's organism and compared it with other members of the group including *B. subtilis*, *B. cereus*, *B. megatherium*, *B. vulgatus*, *B. mesentericus*, *B. mycoides*, and *B. malabarensis*. As a result of this work he came to the conclusion that *B. siamensis* was identical with *B. cereus*. For identification Clark limited himself to morphology, cultural characteristics and pathogenicity for guinea pigs.

The following case, recently seen on the Obstetrical Service of Bellevue Hospital, is reported here because it illustrates infection with one of the aerobic spore-forming bacilli and because opportunity for thorough investigation of the responsible organism existed.

C. S., 19 years of age, white, was admitted to Bellevue Hospital on Dec. 30, 1938, at term with her first pregnancy. The patient had been observed in the prenatal clinic throughout the last six months of her pregnancy and, because of some question in the minds of several examiners as to the adequacy of her pelvis, stereoscopic x-rays had been taken. The results of a study of these plates indicated that the pelvis was small and gynecoid in architecture with slight android tendencies, and a fair mid-pelvis and outlet. Measurements in the precision stereoscope revealed a true conjugate of 10 cm., a transverse of the inlet of 11.5 cm., and an interspinous of 9 cm. The patient's Wassermann was negative and her course throughout pregnancy had been normal.

The patient sought admission because of the onset of lower abdominal cramps and backache eighteen hours before. These pains were not very strong. Examination at the time of admission revealed that the uterus was enlarged to the size of a term pregnancy and the weight of the fetus was estimated to be from 6½ to 7 pounds. The head was dipping into the pelvis in the R.O.A. position. Fetal heart sounds were of good quality. The blood pressure was 110/80, urine showed a trace of albumin, and red blood cells numbered 5 M with 96 per cent hemoglobin (Dare).

\*This study was aided by a grant from The Commonwealth Fund.

rods, measuring 3 to 5 micra in length by 1 micron in width. The ends, in contrast to the morphologic characteristics of the anthrax bacillus, were rounded. The bacilli, from liquid medium, were found singly, in pairs and in chains. In hanging drop preparations they were seen to be motile in a slow and stately manner. Flagella stains revealed that the organism possessed peritrichate flagellae, and spore stains showed large equatorial ellipsoidal spores. The organism possessed no capsule and was positive in its reaction to the Gram stain. With methylene blue, staining was uneven. The organism was aerobic and facultatively anaerobic.

*Cultural Characteristics.*—On agar plates, growth was exceedingly rapid, and, within five hours, definite colonial characteristics made their appearance. The colonies were large, spreading, raised, grayish white, dull and opaque. The surface was finely granular and exhibited a rhizoid appearance similar to that described for *Bacillus mycoides*. The colonies spread so rapidly that the advancing feathery, snow-crystal edge of one frequently overlapped an adjacent colony.

In meat infusion broth growth was likewise rapid with but slight turbidity. Growth at first seemed limited to the surface of the broth where a tough, leathery, grayish wrinkled membrane formed. Somewhat later the membrane sank to the bottom of the tube. On fresh horse blood agar, the colonies were slightly more regular. Slight hemolysis was noted after four days' growth and a distinct odor of ammonia was perceptible. The organism caused the liquefaction of gelatin in a stab culture.

*Biochemical Reactions.*—In liquid medium containing 1 per cent of the individual sugars, the organism fermented glucose, maltose, and sucrose with the production of acid but no gas, and failed to ferment inulin, salicin, lactose, and mannite. In litmus milk it caused decolorization and slow peptonization. Washed organisms in the presence of fresh glucose broth caused incomplete reduction of methylene blue in two hours. The supernatant fluid, however, caused complete reduction of methylene blue in thirty minutes, indicating the elaboration of a reducing agent by the organism. The negative methyl red test indicated that the final pH attained in 0.5 per cent dextrose broth after four days' incubation was more than 4.5. In 1 per cent peptone water the organisms were unable to produce indole. In common with other saprophytic organisms which break down proteins, this organism produced ammonia which was most distinctly perceptible on solid media. In addition, small amounts of  $H_2S$  were produced as determined by the lead acetate test.

The organism failed to reduce nitrates to nitrites, did not produce acetylmethyl carbinol, and did not produce catalase.

*Experiments on Pathogenicity.*—It is undoubtedly true that the organism isolated from the blood stream, uterus, and abdominal abscess was the cause of the pathologic process in our patient. Such being the case, experiments were undertaken to determine whether the organism was pathogenic for animals.

resonance over the right scapular region and diminished breath and voice sounds at the right apex anteriorly. The left lung was clear. The abdomen was slightly distended with moderate tenderness over the fundus uteri which was still palpable at the level of the umbilicus. In addition, there was some tenderness over the entire lower abdomen. Early pneumonia was suspected and the possibility of developing parametritis was also considered. The symptoms and temperature persisted throughout the next day and abdominal examination revealed a tender, fluctuant mass rising to the level of the umbilicus and extending five inches to each side of the midline. It was thought probable that what had been thought to be fundus was in reality the mass now interpreted to be cellulitis of the abdominal wall secondary to parametritis. The patient was given a third transfusion of 500 c.c. of whole blood without reaction. The following day she noted severe dysuria, and the urine specimen obtained that morning possessed a strong fecal odor and showed a thick foul-smelling sediment. This consisted of much amorphous and granular material and numerous clumps of pus cells. It was believed that the abscess of the parametrium had ruptured into the bladder. Further examination showed well-demarcated fluctuation in the lower abdominal wall up to the umbilicus. On pelvic examination, soft induration was noted in the fornices. The fundus, as such, could not be made out. A diagnosis of parametritis with dissecting abscess of the abdominal wall was made and incision and drainage was advised. Four grams of sulfanilamide daily was recommended because of the marked cystitis. Red blood count was 5.1 M; Hg, 65 per cent; white blood count, 20,850 with 90 per cent polymorphonuclear neutrophils. Urine culture was again reported positive for *B. coli* and staphylococci. On incision of the parametrial abscess, 1,500 to 2,000 c.c. of foul, creamy yellow pus containing gas bubbles was evacuated. After drainage, the cavity was found to extend behind the space of Retzius and a cigarette drain was inserted into this area. The temperature on the next day dropped to 99° F. After irrigating the bladder with methylene blue, the abdominal dressings were stained with the dye, thus proving fistulous communication between the bladder and the abscess cavity. For the next two days the temperature remained at a level of 100° F. and aerobic and anaerobic blood cultures, repeated, revealed the continued presence of the same gram-positive spore-forming bacillus. The same organism in association with an anaerobic streptococcus was isolated from the pus evacuated from the abscess at operation.

Drainage continued from the abdominal wound but the temperature dropped to normal on the twenty-second post-partum day (fifth post-operative day). The drain was shortened gradually and bladder irrigations with 1 per cent methylene blue were utilized twice daily. Drainage diminished gradually, and the wound was irrigated with hydrogen peroxide by means of a small catheter. Definite clinical improvement now became manifest. On the thirteenth day postoperative, blood was drawn to test for precipitins and agglutinins against the organism which had been present. It was at this time that the temperature again rose to 104° F., accompanied by the onset of chills and right costovertebral flank tenderness. The clinical course, urinary findings, and lack of evidence of uterine infection made the diagnosis of pyelitis obvious; urine culture showed the presence of *B. coli*. Despite sulfanilamide (3 gm. daily), signs and symptoms of pyelitis persisted for the next week and the temperature then gradually subsided so that five days later it was normal.

Cystoscopy performed before discharge revealed a small slit  $\frac{1}{2}$  cm. in length situated on the left lateral bladder wall. Pelvic examination was completely negative and the abdominal wound was well healed. The patient was discharged on the forty-ninth post-partum day, thirty-two days after operation.

#### DESCRIPTION OF THE ORGANISM

*Morphology.*—The organisms isolated in pure culture from the blood stream and uterus in the several cultures mentioned and found in association with an anaerobic streptococcus in the culture of the pus, were identical in all instances. They were straight or slightly curved

The foregoing experiments suggested the determination of the minimum lethal dose. The following table indicates the results of such an experiment. All injections were made intraperitoneally.

TABLE I

AMOUNT 24-HOUR WHOLE CULTURE	RESULT
0.02	S
0.04	S
0.06	S
0.08	S
0.10	S
0.14	D within 12 hr.*
0.16	D within 12 hr.*
0.18	D within 6 hr.*
0.20	D 2½-5 hr.*
0.30	D 2½-3 hr.*
0.40	D 2½-3 hr.*
0.50	D 2½-3 hr.*

\*The above represents the results of several experiments in each of which the killing time varied somewhat. Hence, range of such time is indicated in the case of animals dying as a result of inoculation.

While the great majority of mice inoculated with quantities of culture varying from 0.15 to 0.18 c.c. died, a few such animals survived. In all cases where amounts of 0.20 c.c. or over were given, all the animals died and organisms were recovered from the peritoneal cavity, pleural cavity and heart's blood.

It is interesting to describe the chain of events following injection and preceding death. About ten minutes after injection, definite hyperesthesia was present and the animals appeared irritable and excited. In a short time muscle spasm began to be apparent especially in the hind legs, which were extended convulsively, raising the animal. This effect gradually spread to the forelegs so that the abdomen was raised from the cage floor and parallel to it. Opisthotonos now became apparent, the animal appearing to stretch slowly, the back arching concavely, and the abdomen touching the cage floor. These convulsive seizures lasted about half an hour, after which the mouse became quiet and definitely hypesthetic. The hair became ruffled and the animals, appearing very ill, huddled together as though for warmth. They showed complete disinterest in food and died quietly without convulsions, and frequently maintained the same position they had assumed prior to death.

#### PRELIMINARY PROTECTION TESTS ON MICE

(a) *By Means of Sulfanilamide.*—It was first attempted to protect mice by means of sulfanilamide. Since previously it had been determined that therapeutically adequate doses of sulfanilamide (in the case of hemolytic streptococci), injected intracutaneously, killed the mice frequently, it was determined to delay absorption of the drug by means of suspending it in olive oil. The drug was carefully ground and suspended in olive oil so that 0.6 c.c. contained 10 mg. of sulfanilamide. The drug was administered in two blebs of 0.3 c.c. each into

*Pathogenicity for Mice.*—The organism is pathogenic for mice. The intraperitoneal injection of 0.5 c.c. of twenty-four-hour culture and even the injection of similar amounts of old refrigerated culture, kills a 20 gm. mouse in two and one-half to six hours. This fact immediately raised the question as to whether the animals died from a pre-formed toxin or as the result of bacterial growth and true infection. In all cases of animals dead after inoculation, living organisms in pure culture were recovered from the site of inoculation, from the pleural cavity and from the heart's blood. The fact that death occurred so rapidly, however, led to the belief that a toxic effect might be of greater importance than the infection itself. Consequently, Berkefeld filtrates of twenty-four-hour cultures were made and mice were inoculated with 0.5 c.c. of the filtrate, shown by plating to be sterile. Such mice survived for four days while control mice, inoculated with whole culture, all died within six hours. In addition, a mouse inoculated with Berkefeld filtrate which had been heated to 80° C. for one hour survived. However, we realized that filtering through a Berkefeld and heating might adversely affect any toxin that might be present, and so the following experiment was performed:

A twenty-four-hour culture was divided into two parts. To one portion, formalin was added to a final concentration of 0.6 per cent. Both portions of the culture were then incubated at 37° C. for four hours and 0.5 c.c. of each was injected into mice. A similar quantity of 0.6 per cent formalin in sterile broth was injected into a third mouse as a control. Control platings, taken just before injection, revealed the formalinized culture to be sterile and the unformalinized culture to contain many colonies. While the mouse inoculated with the unformalinized culture died in six hours, the other animals survived.

A further experiment was run with centrifuged culture. Mice were injected with the supernatant fluid of an eighteen-hour culture, and despite the fact that this fluid was not sterile, the animals survived. In the case of a guinea pig which received 2.5 c.c. of the supernatant fluid, death occurred after eight days. All animals which received 0.5 c.c. doses of the washed and rewashed sediment of such an eighteen-hour culture died in two and one-half hours, and living organisms in pure culture were obtained from the peritoneal cavity, the pleural cavity and the heart's blood.

A mouse which had received supernatant fluid and which had survived was killed, and platings of the peritoneal washings revealed 200 colonies of the organism per c.c. Five-tenths cubic centimeter of this peritoneal washing was injected into a second animal which survived and from whose peritoneum no organisms could be secured. The experiment suggests that overwhelming numbers of the organisms are essential to produce death and that small numbers are easily removed, probably by means of phagocytic action. This observation is further borne out by the fact that repeated animal passage following the administration of sublethal doses of whole culture fails to cause death in animals subsequently inoculated with peritoneal washings of such mice.



## DISCUSSION

Transfers of the organism isolated from this case were submitted to the American Type Culture Collection for identification. The opinion of Mr. N. R. Smith<sup>11</sup> was that the organism "agrees in all respects" with the *Bacillus cereus* cultures which he and Clark<sup>10</sup> described. On a cultural and morphologic basis there seems to be little doubt of the resemblance, although culturally it is difficult to distinguish *B. cereus* from *B. mycoides*. In an attempt to classify our organism more accurately, typical strains of *B. cereus* and *B. mycoides* were secured from the collection and both whole cultures and HCl extracts of the cultures were tested with serum prepared against the organisms we had isolated. The results are tabulated in Tables II and III.

TABLE II. AGGLUTINATION TESTS

CULTURE	PREPARED ANTISERUM*					
	UNDIL.	1:10	1:20	1:40	1:80	1:160
Patient's	+++	++++	++++	++++	++++	++++
Mycoides	+++	+++	+++	+	-	-
Cereus	-	-	-	-	-	-

\*Made by inoculating rabbits with heat killed cultures of the organism obtained from the patient.

TABLE III. PRECIPITIN TESTS

	EXTRACTS								
	PATIENT'S			MYCOIDES			CEREUS		
	UNDIL.	1:4	1:16	UNDIL.	1:4	1:16	UNDIL.	1:4	1:16
Prepared antiserum	++++	++++	++++	-	-	-	-	-	-

From the above tables it is seen that cross agglutination occurs between antiserum prepared against the organism isolated from the patient and cultures of *B. mycoides*. No cross agglutination occurs with cultures of *B. cereus*. No cross precipitin tests were observed with either organism. How much significance should be placed on these findings it is difficult to say.

In tests for pathogenicity, using doses of 0.3 c.c. of twenty-four-hour culture, it was found that mice receiving cultures of *B. cereus* died in eight to ten hours. Mice injected with cultures of *B. mycoides* survived. It is worth noting that the growth of these two organisms was not nearly as profuse as the growth of the organism being investigated, and therefore comparable quantities of culture did not contain comparable numbers of organisms.

So far as the ultimate classification of this organism is concerned, we are still at a loss as to its proper place.

## SUMMARY

1. A case of parametrial abscess and septicemia following childbirth is reported.

2. An organism, isolated repeatedly in pure culture from the blood stream and in mixed culture from the uterus and parametrial abscess,

the skin of the abdomen. Control animals treated in this manner survived. Mice given 10 mg. of sulfanilamide followed in two hours by 0.2 c.c. (1 minimum lethal dose) of whole twenty-four-hour culture intraperitoneally all died within six hours. It was thought that probably the concentration of sulfanilamide was not high enough to be effective, so that in a second experiment, mice were injected with 10 mg. of the drug daily for three days and on the third day, immediately after the third dose of sulfanilamide, were given 0.3 c.c. of whole twenty-four-hour culture intraperitoneally. These animals died within six hours, and living organisms were recovered in all cases. We realize that these experiments are inadequate to demonstrate the effect or lack of effect of sulfanilamide, for no analyses to determine concentration of the drug in the blood were undertaken. Likewise, there were no variations in the dose of the drug between the dose employed and the lethal dose of sulfanilamide.

(b) *By Means of Antibacterial Serum.*—Antibacterial serum was prepared by the injection of rabbits as follows:

Two hundred cubic centimeters of the twenty-four-hour broth culture of the organism were centrifuged and the sediment was resuspended in 5 c.c. of saline. This was heated to 60° C. for one hour, incubated at 37° C. for twenty-four hours to permit spores to germinate, and again heated to 60° C. for one hour. Tests for sterility revealed no living organisms. The suspension was left in the refrigerator and just before use was diluted 1:20 with saline. Rabbits received four series of five injections each, beginning with a series of 1 c.c. daily followed by a 2 c.c., a 4 c.c., and a 6 c.c. series with five-day intervals between each series. These series were followed by six daily intravenous injections (0.5, 2, 3, 5, 6, and 6 c.c., respectively, of living organisms) the virulence of which had been raised by mouse passage. Five days after the last injection the animal was bled from the heart and the serum collected.

Nine mice were divided into three groups. The first group received intraperitoneal injections of 0.3 c.c. of fresh twenty-four-hour culture plus 1 c.c. of normal rabbit serum. The second group received organisms plus antiserum in the same amounts, and the third group received a mixture of organisms and antiserum which had been allowed to incubate at 37° C. for one hour prior to injection. All mice in the last two groups survived while two of the three control mice died within eight hours. It seems, therefore, that there is definite protection afforded by antibacterial serum in the amounts used, although the test animals received only 1½ minimum lethal dose of the organisms.

Protection tests along similar lines with convalescent serum obtained from the patient on the twenty-fourth day of her illness failed completely to demonstrate any protective activity.

*Serologic Tests.*—Rabbit antiserum diluted 1:1 when mixed with HCl extracts of the organisms undiluted and diluted 1:4 and 1:16 gave positive precipitin reactions. Convalescent patient's serum failed to show the presence of agglutinins or precipitins against the organism.

typical case presents hydramnios, a large friable placenta, dark yellow amniotic fluid and golden yellow vernix.<sup>2</sup> Examination of the fetus reveals enlargement of the heart, liver, and spleen and extensive extramedullary hematopoietic centers. Hemosiderin may be present in the liver, but usually is not found in the spleen. Blood examination reveals a severe anemia with many immature cells of both the red and white series. In icterus gravis neonatorum, the most characteristic finding at birth is a marked pallor of the skin and mucous membranes which is soon followed by the development of increasing icterus. The placental changes may be identical with those of congenital hydrops. Except for the edema the findings on examination are identical with those of congenital hydrops.

Treatment in all types is directed toward stimulation of the bone marrow and decreasing the severity of the anemia until the hematopoietic tissues can function normally of their own accord. The most effective manner of accomplishing this end is the use of frequent small transfusions of citrated blood.

The prognosis in all these cases is grave. As has been stated above, infants with congenital hydrops are usually stillborn and if they are born alive death usually occurs within forty-eight hours. The prognosis in icterus gravis neonatorum and congenital anemia is poor even with intensive therapy.

A review of the literature by Diamond, Blackfan, and Baty<sup>1</sup> shows that congenital hydrops has been recognized for a great many years. Ballantyne<sup>3</sup> (1898) reported 70 cases taken from the world's literature since 1614. Schritte (1910) first described the hematopoietic disturbance in congenital hydrops. The first mention of the pathologic changes was made in a report by Buchan and Comrie<sup>4</sup> (1909), who noted erythroblastosis, hepatomegalia, splenomegalia, and areas of extramedullary hematopoiesis in several cases of icterus gravis neonatorum. Since then there have been several completely studied cases of all three types added to the literature, notably those of Hueper and Mullen,<sup>5</sup> Ferguson,<sup>6</sup> Plaut and Bullard,<sup>7</sup> and Wanstrom.<sup>8</sup>

Four cases of erythroblastosis fetalis are reported here; one icterus gravis neonatorum, two congenital hydrops (a stillborn infant and one who lived one hour), and an infant who died four hours after birth. The diagnosis on the last baby was made by pathologic examination. All the infants were delivered in the University of Michigan Maternity Hospital, three of them within a period of one month.

CASE 1.—The mother, aged 22 years, was a gravida v, para iv, the former pregnancies having terminated as full-term normal spontaneous deliveries of normal infants. In 1936 a diagnosis of congenital syphilis and interstitial keratitis was made in this hospital and she was treated with five intravenous injections of arsphenamine and five intramuscular injections of bismuth. Advice to continue treatment with her local physician was not heeded. Upon questioning she stated that all her babies had been "very yellow" soon after birth, but there had been no apparent morbidity. The family history was otherwise negative.

*Antenatal History.*—The mother had measles, diagnosed by her local doctor, about three weeks before delivery. She had noted that fetal movements had been feeble all through the pregnancy. There was no evidence of toxemia on admittance to the hospital, but she had received no antenatal care and was first seen in labor. The blood Kahn test on admittance was positive.

is described as to: (a) Morphology and staining properties, (b) cultural characteristics, (c) biochemical reactions, (d) pathogenicity, and (e) serologic reactions.

3. This organism corresponds closely to the *B. cereus* described by Clark and also bears some resemblance to *B. mycoides* as far as many of its cultural, morphologic and serologic characteristics are concerned.

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## ERYTHROBLASTOSIS FETALIS

### A REPORT OF FOUR CASES

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**E**RYTHROBLASTOSIS FETALIS is a disease of the newborn infant characterized by marked dysfunction of the hematopoietic and hemolytic systems, resulting in (1) failure of maturation of the erythrocytes or the overproduction of immature forms; (2) extrusion of abnormal numbers of immature erythrocytes into the circulating blood; and (3) abnormal destruction of erythrocytes. According to Diamond, Blackfan and Baty,<sup>1</sup> it may occur in three distinct forms: (1) congenital anemia of the newborn in which severe anemia is the most pronounced factor; (2) icterus gravis neonatorum in which the anemia is associated with the early onset of a marked icterus; and (3) congenital hydrops or universal edema of the fetus in which anasarca is the most outstanding sign.

Although each of the three types is a definite clinical entity, the group has certain features in common, namely: (1) A familial incidence most frequently noted in icterus gravis neonatorum and congenital hydrops; (2) hepatomegaly and splenomegaly; (3) severe anemia with large numbers of erythroblasts in the circulating blood; (4) extensive extramedullary centers of hematopoiesis, noted especially in the liver, spleen, kidneys, and adrenals; and (5) frequently edema and enlargement of the placenta.

The clinical course of each of the three forms is somewhat different. Congenital hydrops reaches its greatest severity in utero and often results in the premature delivery of a stillborn edematous fetus. The

delivery of normal children who are alive and well. The second, a female, has had six pregnancies which terminated as follows: (1) miscarriage at three months; (2) miscarriage at five or six months; (3) and (4) normal spontaneous deliveries of normal infants who are alive and well; (5) miscarriage at three months; and (6) a premature delivery at eight months, the infant living four days. The third, a male, is the father of four children, two of whom died of unknown causes at five months and two years, respectively; the remaining two children are alive and well. The fourth, a female, has had two pregnancies, both terminating in the normal spontaneous delivery of full-term infants who are alive and well. The fifth, the mother of the patient under discussion, has had four pregnancies which terminated as follows: (1) normal spontaneous delivery of a full-term infant who is alive and well; (2) normal spontaneous delivery of a full-term infant who died in twenty-four hours; (3) normal spontaneous delivery of an eight months' fetus in this hospital. This baby died on the third day with severe jaundice; bile was reported to be present in the cord blood sent to the laboratory for the cord Kahn test. An autopsy was not permitted and no other data are available. The fourth pregnancy terminated in the birth of the abnormal fetus under discussion.

Other family history is noncontributory.

*Antenatal Course.*—The mother, aged twenty-six years, was followed in this clinic during her pregnancy. The blood Kahn test was negative. Late in pregnancy she developed a mild toxemia with ankle edema, one-plus albuminuria and a blood pressure elevation to 150/90 mm. Hg. During the latter part of the prenatal period she complained of a constant dull aching pain in the lower right quadrant which was not easily relieved.

*Clinical Course.*—Contractions began spontaneously and the patient was delivered of an edematous fetus following a labor lasting four hours and thirty-five minutes; considerable difficulty was encountered in the extraction of the fetus, because the marked edema prevented normal extension of the head. During the delivery a cervical dislocation was produced as was demonstrated at the time of autopsy. There was one feeble respiratory gasp after the head had been delivered, but further attempts at respiration were not noted despite vigorous attempts at resuscitation. Examination of the fetus revealed marked edema with a tremendously distended abdomen, the eyes were swollen shut, and the ears were pushed out at right angles to the edematous scalp. The total length was 43.5 cm., the circumference of the chest 33 cm., and of the abdomen 38 cm.

Following the extraction of the infant an unusually large amount of yellowish green amniotic fluid was lost. The placenta measured 31 by 24 by 5 cm. and was very soft, pale, and friable. The cord Kahn test was negative. Microscopic examination of the placenta revealed slight fibrosis and increased cellularity of the chorionic stems without evidence of hematopoietic activity.

*Autopsy.*—The gross examination revealed the marked anasarca described above, but an average amount of edematous panniculus. No developmental anomalies were noted. There was a dislocation between the fourth and fifth cervical vertebrae, with fresh blood around the cord from the foramen magnum to the level of the sixth dorsal segment. There was marked edema of the scalp, periosteum, and brain with increased subarachnoid fluid.

The thymus was small and appeared normal. The heart measured 4.5 by 3.5 by 2.2 cm. and weighed 50 gm. (normal 14 gm.); the pericardial fluid was normal in amount. Further examination of the heart revealed a patent foramen ovale and patent ductus arteriosus. The lungs appeared normal.

The panniculus over the abdomen measured 4 mm. In the abdominal cavity were 225 c.c. of thin yellow ascitic fluid. The spleen measured 6.5 by 3.4 by 1.5 cm. and weighed 18 gm. (normal 8 gm.); there were no lymphoid follicles noted. The gastrointestinal tract appeared normal. The liver measured 11 by 5.5 by 4 cm. and weighed 164 gm. (normal 127 gm.); to gross examination it appeared normal. There was edema of the wall of the gall bladder. The left and right kidneys weighed 11 and 10 gm., respectively and showed remains of fetal lobulations. The pelvic organs appeared normal.

*Clinical Course.*—The labor was uncomplicated. It was noted that on rupture of the membranes about 500 c.c. of clear amniotic fluid were expelled. The placenta measured 14 by 18 cm. and appeared somewhat edematous to gross examination. Respirations were spontaneous and immediate, but extreme pallor of the skin and mucous membranes was noted at birth. About four hours after birth, jaundice was noted and the infant appeared lethargic and stuporous. The jaundice rapidly increased to an intense yellow.

Petechial hemorrhages over the face, abdomen, and extremities appeared on the fourth day. At that time the lower border of the spleen was found to reach the pelvic brim and the liver edge was 5 cm. below the right costal margin. There was a soft blowing systolic murmur over the whole precordium. The hemoglobin was 29 per cent (Sahli), red blood count 820,000 per c. mm., and white blood count 29,000 per c. mm. The blood smear showed a high percentage of immature cells of both the red and white series.

The baby was given 75 c.c. of citrated blood intravenously and 125 c.c. of Ringer's solution that day. A continuous intravenous injection of citrated blood, totaling 250 c.c., was given on the fifth day; on the sixth day 125 c.c. of citrated blood and 100 c.c. of Hartmann's combined lactate Ringer's solution were given, and it was noted at this time that the color of the infant was considerably improved. Eighty cubic centimeters of citrated blood, and 300 c.c. of Hartmann's solution were given on the seventh day, and universal edema was first noted following their administration, the baby having gained from 3,020 gm. to 3,707 gm. in four days. It was felt that the edema was not part of the disease as, when the intravenous fluids were discontinued, the edema disappeared. On the eleventh day, 90 c.c. and on the twelfth day 100 c.c. of citrated blood were given.

Following the institution of treatment, gradual improvement was noted in the condition of the patient, the jaundice became less marked and the infant more alert. One month after birth the spleen was 2 cm. below the left costal margin, the jaundice had disappeared, the evaporated milk formula was being taken eagerly, and there had occurred a weight gain of 214 gm. during the preceding ten days.

*Laboratory Findings.*—The Kahn test for syphilis was negative on the cord blood and on venous blood on the tenth and thirtieth days.

Urine on the tenth day was negative except for large amounts of bile and urobilinogen which was positive in a dilution of 1:500; on the thirtieth day there was only a trace of bile and the urobilinogen was positive in the undiluted specimen only.

The stools on the tenth and thirtieth days were normal, both specimens containing bile.

Blood examination on the twenty-first day showed: hemoglobin 94 per cent (Sahli), red blood count 5,020,000 c. mm., white blood count 12,000 c. mm., the smear showed immature leucocytes and erythrocytes.

The Duke bleeding time was five minutes and fifty-five seconds on the tenth day, and the capillary tube clotting time three minutes and fifteen seconds. Fragility test on the thirtieth day was normal, hemolysis of the erythrocytes beginning at 0.42 per cent and being complete at 0.3 per cent normal saline in the blood of the patient and a normal control.

Roentgen examination of the long bones on the thirtieth day was negative for any evidence of syphilitic involvement.

*Comment.*—A nonsyphilitic infant was born with clinical signs typical of erythroblastosis fetalis, the diagnosis being substantiated by laboratory studies. Complete recovery followed the intravenous injection of a total of 720 c.c. of citrated blood and 525 c.c. of other fluids over a period of eight days.

CASE 2.—The maternal grandmother of this infant had thirteen children, six of whom (the first, second, third, seventh, eleventh, and thirteenth) are living and well. Five pregnancies terminated in miscarriages early in their course. The remaining children were born alive at term. One died on the second and one on the third day of life, both with severe jaundice, but no other information could be obtained.

Of the living children, five have married and had children of their own. The first, a female, has had three pregnancies, all terminating in the normal spontaneous

fants, 10 of whom are alive and well. The eighth baby died on the eleventh day of its life of an unknown cause. No other significant family history was obtained.

*Antenatal Course.*—The pregnancy was entirely uneventful. The patient was first seen in the antenatal clinic two weeks before delivery; during the rest of the antepartum course, no abnormalities developed.

*Clinical Course.*—The mother was delivered of an asphyxiated baby following a normal five-hour labor. The respirations were delayed about twenty minutes, but the heart remained of good quality. Despite vigorous treatment the respirations ceased four hours post partum.

The placenta measured 18 by 21 cm. and appeared normal. The cord Kahn test was negative.

*Autopsy.*—The gross examination revealed a cyanotic infant with a few small petechial hemorrhages in the upper half of the body. There were petechial hemorrhages in the brain and spinal cord.

Upon opening the chest, 20 c.c. of clear yellow fluid were found in the right and 15 c.c. of the same type of fluid in the left thorax. The thymus weighed 18 gm. and surrounded three-fourths of the circumference of the trachea, but there was no evidence of compression. The heart measured 4 by 4 by 2 cm. and weighed 18 gm. Both the foramen ovale and ductus arteriosus were patent. The lungs were partially atelectatic.

The abdomen contained no free fluid. The liver edge was found to be 4.5 cm. below the right costal margin and 6 cm. below the ensiform. The liver measured 13 by 7 by 4 cm. and weighed 154 gm. The spleen and other organs appeared normal.

The microscopic examination showed large areas of hematopoiesis in the lungs, thyroid, thymus, liver, lymph nodes, and cervix, with many immature blood cells of both the red and white series in the circulating blood.

*Comment.*—A nonsyphilitic infant died four hours after birth. Pathologic examination showed erythroblastosis fetalis.

#### DISCUSSION

Although erythroblastosis fetalis may be considered as a definite clinical entity, there are certain other conditions which may simulate the disease and which may be differentiated from it only by complete study of the patient.

Congenital syphilis may resemble the condition. Diamond, Blackfan, and Baty report the birth of a full-term infant with jaundice noted at delivery and mucous membrane pallor during the first week of life. Examination showed enlargement of the liver and spleen, ecchymoses and petechial hemorrhages of the skin, severe anemia and many immature erythrocytes, and leucocytes in the circulating blood. Blood tests for syphilis were positive, and roentgenograms of the long bone showed osteochondritis, suggestive of congenital syphilis. Post-mortem examination revealed changes typical of congenital syphilis, and spirochetes were demonstrated in the tissues.

Infection with sepsis may be followed by severe anemia with immature circulating blood cells and visible jaundice. In these cases there is a temperature elevation, diarrhea, vomiting, and the signs of infection appearing before the blood picture changes.

In hemorrhagic disease of the newborn infant, the anemia depends on the amount of blood lost. Icterus, hepatomegalia and splenomegalia are usually not present, nor is there a marked quantitative change in the blood picture.

The spinal cord showed congestion and edema of the meninges with immature blood cells in the blood vessels. The brain showed post-mortem change and active areas of hematopoiesis. The lungs showed fetal atelectasis without evidence of hematopoiesis. The trachea and larynx were negative except for marked edema. In the thymus there were noted hematopoietic centers scattered through the whole gland. The spleen was markedly congested and showed extensive hematopoiesis. There were areas of hematopoiesis in the serosa of the small intestine and petechial hemorrhages in the serosa and mucosa. There was also hematopoiesis in the serosa of the appendix and colon. The liver showed patchy increase in the stroma of the islands of Glisson with many immature cells of both the red and white series in the stroma and sinusoidal spaces. The adrenals also showed patchy foci of hematopoiesis with patchy cortical lipoidosis. Small hematopoietic foci were noted in the urinary bladder, and increased hematopoiesis was noted in the lymph nodes. Bone marrow from the ribs, sternum, and vertebral bodies showed many immature blood cells.

*Comment.*—A nonsyphilitic infant was born with congenital hydrops. The family history revealed three cases of early severe jaundice with death of the infants, many miscarriages, and several infants who died in the first few days of life. The diagnosis of erythroblastosis fetalis was confirmed by gross and microscopic examination of the fetus.

*CASE 3.—Family History:* The mother, aged 19 years, was a gravida iii, para ii. The two previous pregnancies had terminated in the normal spontaneous deliveries of normal full-term infants who are alive and well. There had been no unusual symptoms during the antenatal course; nausea and vomiting in both pregnancies had been confined to the first trimester. No significant family history was elicited.

*Antenatal Course.*—The mother was first seen in the antenatal clinic four days before going into labor. Nausea and vomiting had occurred daily throughout the entire pregnancy. No fetal movements had been felt in the last three weeks before admittance.

*Clinical Course.*—The patient was delivered of a 2,700 gm., grossly edematous fetus after a twenty-hour labor. Examination of the infant revealed a slow regular fetal heart, with a loud systolic murmur heard over the whole precordium. The liver was palpable in the right lower quadrant of the abdomen, but the spleen could not be felt. The baby did not breathe despite all measures of resuscitation, and after one hour the fetal heart stopped.

The placenta measured 18 by 19 cm. and was pale and edematous with indistinct sulci between the cotyledons. Microscopic examination revealed no evidence of hematopoietic activity.

*Autopsy.*—The gross examination revealed marked edema especially of the scalp. The brain tissue was very soft, but no other abnormalities were noted.

There were 30 c.c. of sanguineous fluid in each side of the thoracic cavity. The thymus was small and appeared normal. The heart measured 4 by 4.5 by 1.8 cm. and weighed 21.5 gm. Both the ductus arteriosus and the foramen ovale were patent. The lungs were partially atelectatic.

The panniculus over the abdomen was minimal in amount. Upon opening the abdominal cavity it was noted that the liver edge was 5.5 cm. below the right costal margin. In the abdominal cavity there were 100 c.c. of sanguineous fluid. The spleen measured 6 by 3.5 by 1.5 and weighed 18.5 gm. No lymphoid follicles could be made out. The liver measured 12 by 9 by 3.5 and weighed 185 gm. The remaining organs appeared normal.

The microscopic examination showed numerous immature blood cells of both the red and white series in the circulating blood with areas of hematopoiesis in the spleen, adrenals, kidneys, generative organs, lymph nodes, trachea, and bone marrow.

*Comment.*—An infant who lived one hour was born with erythroblastosis fetalis. The family history was noncontributory. The clinical diagnosis was confirmed by pathologic examination of the fetus.

*CASE 4.*—The mother, aged 42 years, was a gravida xii, para xi. The previous pregnancies had all terminated in the normal spontaneous deliveries of full-term in-



# SUBCUTANEOUS IMPLANTATION OF COMPRESSED CRYSTALLINE THEELIN PELLETS IN THE TREATMENT OF MENOPAUSAL CASES\*

## PRELIMINARY REPORT

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and Hospital)*

USUALLY, in the past, estrogenic preparations have been administered orally and by hypodermic or intramuscular injection. By these methods frequently repeated doses have been necessary, over rather long periods of time. With the hope of obtaining a more prolonged estrogenic effect, we have thought it worth while to investigate a new method of estrogen administration, whereby pellets of compressed crystalline estrogenic substances are implanted subcutaneously to be absorbed slowly over a long period of time. Such a method has been described by Parkes and Deansley<sup>1</sup> and found effective in obtaining prolonged hormonal stimulation in animals. Consequently we have treated twenty-one patients with menopausal symptoms by the subcutaneous implantation of estrogenic pellets. In an effort to evaluate this type of therapy, we have (1) observed the modification of subjective symptoms such as hot flushes; (2) determined in all cases the urinary level of estrogen before and after pellet implantation, in order to obtain some idea of the rate and duration of the absorption of estrogenic substance from the pellets; (3) determined the urinary level of follicle-stimulating hormone before and after treatment in order to estimate the effect exerted by the absorbed estrogen on hypophyseal activity; and (4) in ten cases, studied biopsies of the vaginal mucosa obtained before and after treatment in order to ascertain the physiologic potency of the absorbed estrogen on the genital tract epithelium.

## TECHNIQUE

Pellets of pure crystalline estrogens have been made by direct compression of the crystals in drilled, machine ground, steel plates. The pellets used have been 1.83 mm. in diameter, 2.0 to 3.0 mm. in length, and 5.0 to 6.0 mg. in average weight. The estrogen pellets have been sterilized in a dry steam autoclave at 250° F. under 15 pounds of pressure for thirty minutes. Implantations in our patients have been made through a twelve gauge hollow needle fitted with a stylette. The pellets are loaded into the pointed end of the needle, and the needle passed through the skin after procaine infiltration. Pressure on the stylette as the needle is withdrawn deposits the pellets in the subcutaneous tissues. Sterile technique is, of course, observed throughout the implantation procedure.

*Dosage.*—We have given in a single implantation from 3 to 10 pellets with a total weight of 8.0 to 50.0 mg. Several patients have received two or more implantations. In all, 40 implantations of estrogenic pellets have been made in 21

\*Supported by a Research Grant from Parke, Davis and Company.

Congenital malformation of the bile ducts may be differentiated by the presence of acholic stools, the absence of anemia and immature blood cells, and a later appearance of the jaundice.

Physiologic icterus usually appears on the third day of life and is absent at the end of a week. The jaundice is less severe, there is no change in the size of the liver or spleen and the blood picture is normal.

Because there are so many other conditions which may simulate erythroblastosis fetalis, it is imperative that a patient presenting an early onset of jaundice associated with hepatomegalia, splenomegalia, and a blood picture typical of the disease be completely studied to rule out other conditions which may produce these signs.

Transfusion of citrated blood should be instituted as soon as the condition is recognized and must be continued until the normal function of the bone marrow is established, if any improvement in the condition of the patient is to be expected.

#### SUMMARY

1. Four cases of erythroblastosis fetalis, two of congenital hydrops, one of icterus gravis neonatorum with recovery, and one in an infant who died four hours after birth are reported. Blood Kahn tests on all were negative.

2. An interesting family history of many miscarriages, early infant deaths, and the death of three infants with severe jaundice was obtained from the mother of one of the cases of congenital hydrops. The family history in the other cases was not conclusive.

3. Post-mortem examination of three of the cases revealed hepatomegalia, immature cells in the circulating blood, and extramedullary centers of hematopoiesis. Two of the infants had splenomegalia.

4. Following frequent small transfusions totaling 720 c.c. of citrated blood to the patient with icterus gravis neonatorum, the liver and spleen gradually decreased in size, the jaundice diminished, the anemia improved, and the patient was apparently quite fully recovered in thirty days.

5. Erythroblastosis fetalis may be suspected if the placenta is large, pale, and friable, and there is an increased amount of amniotic fluid which may or may not be yellow tinged.

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TABLE I. RECORD OF CASES\*

CASE	AGE	TYPE OF MENOPAUSE	TOTAL WT. OF PELLETS IN MG.	TOTAL NO. OF PELLET IMPLANTATIONS	ESTRO. BEFORE TREATMENT. R.U.	ESTRO. AFTER TREATMENT. R.U.	F.S.H. BEFORE TREATMENT. R.U.	F.S.H. AFTER TREATMENT. R.U.	FLUSHES BEFORE TREATMENT. Q.D.	FLUSHES AFTER TREATMENT. Q.D.	TIME AFTER FIRST IMPLANTATION. WK.	TIME AFTER LAST IMPLANTATION. WK.
1†	48	Phys. No. 135079	44.1	2	0	6.6	0	0	15	0-4	10	7
2†	48	Phys. No. 165878	67.2	2	0	14.4	0	0	10-16	0-3	21	6.5
3†	50	Phys. No. 166020	65.8	2	0	9.9	25	0	20-30	0-5	13.5	8.5
4†		Phys.	64.4	2	4.1	15.6	100	0	15-20	0-2	9	2
5†	48	Phys. No. 29821	40.2	2	0	19.8	100	0	3-4	None	25	10.5
6†	57	Phys. No. 147209	50.2	2	0	--	25	0	3-4	None	12.5	8.5
7†	52	Phys. No. 160865	42.5	1	0	5.8	0	0	6-8	2-3	3	--
8†	53	Phys. No. 166482	22.9	1	0	10.6	0	0	10-12	0-1	2	--
9†	44	Phys. No. K-17175	19.8	1	0	8.0	25	0	4-5	1	10	--
10†	42	Phys. No. 119266	22.2	1	0	7.7	100	0	3-4	None	10	--
11†	52	Phys. No. 155294	22.0	1	0	2.0	25	50	10-12	8-10	4.5	--
12†	44	Phys. No. 122378	19.8	1	0	--	25	0	5-6	None	4.5	--
13†	53	Phys. No. 166295	27.2	1	0	2.6	50	25	3-5	--	4.5	--
14†	46	Cast. No. 176205	84.6	5	0	4.0	100	50	20-30	0-4	37	12.5
15†	39	Cast. No. 74392	121.0	4	3.8	15.5	25	50	18-20	0-15	20	6.5
16†	24	Cast. No. 157410	35.8	2	0	4.8	100	100	10-15	1-2	8	3.5
17†	43	Cast. No. 101903	50.0	1	0	9.9	100	0	15-20	7-8	7.5	--
18†	31	Cast. No. 143429	22.0	1	0	5.0	0	25	3-5	2-3	8	--
19†	24	Cast. No. 155639	22.7	1	0	4.5	100	0	8-10	2-3	16	--
20†	31	X-ray No. 155994	42.1	2	0	4.3	25	0	8-10	2-6	17	7.5
21†	47	X-ray No. 111919	45.7	2	0	3.0	50	--	10-12	1-5	10.5	4

\*The designation "0" under estrogen indicates less than 2.0 R. U. per twenty-four-hour specimen, and "0" under follicle-stimulating hormone (F. S. H.) indicates less than 25 R. U. per liter of morning urine, each being the lower threshold, respectively, of the methods used. In three of these cases an additional implantation has been made, but the follow-up assays have not yet been completed, and so these three implantations are not included in this table.

†From Johns Hopkins Hospital.

‡From a private patient of Dr. H. S. Everett.

patients. In 34 instances, pellets of theelin\* have been used, and in 6 instances pellets of other estrogenic crystals.

### MATERIAL

The 21 patients treated include 13 cases of physiologic menopause, 6 cases of operative castration, and 2 cases of radiation menopause. Seven of these patients had previously been treated with hypodermic injections of estrogens in oil, and 2 patients had received radiation of the hypophysis with only temporary relief of symptoms.

### METHODS

Estrogen determinations have been made on twenty-four-hour specimens of fresh urine. The twenty-four-hour benzene extraction method, with preliminary acid hydrolysis, has been used.<sup>2</sup> Estrogenic activity of the olive oil extract has been determined by its effect on the vaginal smear of the mature castrate rat.

Determinations of follicle-stimulating hormone levels have been made on concentrated morning specimens of urine, extracted by the alcohol precipitation method.<sup>3</sup> The gonadotropic activity of the aqueous extract has been determined by the follicle-stimulating effect on the immature (eighteen- to twenty-day-old) rat ovary, as seen in serial sections.

Vaginal biopsies have been obtained by means of a special biopsy clamp, sectioned after formalin fixation, and stained with hematoxylin and eosin.

A total of 179 estrogen and follicle-stimulating hormone assays have been completed thus far on urine specimens from the twenty-one patients studied. A total of 31 vaginal biopsies from 10 patients have been studied.

### RESULTS

1. *Effect on the Urinary Estrogen Level.*—In 19 of the 21 cases studied, no estrogen (or less than 2.0 R.U. per twenty-four-hour specimen, the threshold of the method used) was found in the urine before pellet implantation therapy was begun. In 2 cases 4.1 and 3.8 R.U., respectively, were found in twenty-four-hour specimens before treatment.

In all cases the urinary estrogen level became elevated following implantation of estrogen pellets. The average level reached after treatment has been between 8 and 10 rat units per twenty-four hours. This elevation has already continued in most cases for ten weeks or more. In one case the urinary estrogen is still elevated sixteen weeks after a single implantation of pellets. In another case in which 17.0 mg. of crystalline estrogen in 6 pellets were implanted, the estrogen level in the urine rose from less than 2.0 R.U. to more than 9.9 R.U. per twenty-four hours, and at a determination done fourteen and one-half weeks after implantation, this level was still maintained. In this case, an additional implantation of 23.2 mg. of theelin in 7 pellets was made at the end of fourteen and one-half weeks, and the urinary estrogen ten and one-half weeks later was 19.8 R.U. per twenty-four hours. So in this case, 30.2 mg. of theelin, given in two implantations, have already maintained the urinary estrogen level at a relatively high point for six months.

Estrogen apparently does not appear in the urine for several days following pellet implantation. In one case daily urinary estrogen determinations were done, and no estrogen was found until the fourth day after treatment with 27.2 mg. of theelin. In most cases the peak level of urinary estrogen excretion has not been reached before the fifth or sixth week following pellet implantation. Considerable variation in different patients has been encountered in the amounts of estrogen excreted in the urine after approximately equal doses of pellets. Since these levels are fairly constant in a given patient, it seems likely that this variation in excretion depends either on factors influencing absorption of the pellets or on some as yet unknown factors active in the process of estrogen metabolism.

2. *Effect on the Urinary Follicle-Stimulating Hormone Level.*—Of the 21 cases studied, 7 had a urinary follicle-stimulating hormone level above 100 rat units per liter before treatment, two had levels between 50 R.U. and 100 R.U. per liter, 6 between 25 R.U. and 50 R.U. per liter, and 6 below 25 R.U. per liter.

\*Supplied by Parke, Davis and Company.

estrogens, to elevate the urinary estrogen level and to produce relief of menopausal symptoms for relatively long periods of time. We feel that the method is simple enough that it can easily be carried out as an office procedure. The duration of effective estrogen supply is long enough to recommend this method of estrogen administration over the oral and hypodermic injection methods in general use heretofore.

We recognize the limitations of the value of urinary hormone assays as an index of hormone metabolism, but feel that the definite and prolonged increase of urinary estrogens in our patients after treatment indicates at least that the estrogen is absorbed from the subcutaneous pellets, and that the disappearance of follicle-stimulating hormone from the urine in 10 of 15 cases suggests that this absorbed estrogen exerts a beneficial inhibiting influence on the hypophysis in postmenopausal cases. The estrogen as absorbed from the compressed subcutaneous pellets is an effective stimulus of growth in the vaginal mucosa. It seems then that estrogenic substances administered by this method lose none of the physiologic properties of estrogens administered in other forms, and that this method, therefore, can be advantageously employed in any case requiring prolonged estrogenic stimulation.

#### SUMMARY

1. A method of subcutaneous estrogenic pellet implantation is described.
2. A preliminary series of 21 menopausal cases, in which the patients were treated by this method, is reported.

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The generally accepted view is that postoperative phlebitis is due to infection and that slowing of the blood stream and increase in the number of blood platelets cause the initial thrombosis. Most cases of phlebitis are treated by strict immobilization for six weeks to prevent emboli. In 1934 Leriche advanced the physiopathologic conception of phlebitis in which he maintains that the edema of phlebitis is not due to simple stasis but that the parietal venous changes irritate the perivenous sympathetic nerves, as a result of which there is reflex arterio-capillary vasoconstriction. Since there is a hyperirritability of the perivenous sympathetics, the thing to do is suppress it. Most of the vasomotor reflexes of the lower limbs pass through the ganglia of the lumbar sympathetic chain. Hence, blockage of this chain by anesthesia will successfully suppress disturbances due to spasms. On this basis infiltration of the lumbar sympathetic is excellent treatment for postoperative phlebitis. Démarez reports three cases of phlebitis treated by this means, and he is enthusiastic about this new advance in the therapy of phlebitis. When the infiltration is carried out early, pain disappears, the temperature drops, and edema either does not appear or is minimal.

J. P. GREENHILL.

Following the implantations of estrogenic pellets, the urinary follicle-stimulating hormone level dropped below 25 R.U. per liter in 10 of the 15 patients who had an initial elevation above 25 R.U. per liter. In these cases follicle-stimulating hormone disappeared from the urine between the second and fourth week following treatment, and has remained absent as long as twenty-five weeks. These patients are still under observation, and the depression of the urinary follicle-stimulating hormone level has persisted to date.

In 5 cases the amounts of urinary follicle-stimulating hormone has continued to be excessive in spite of the fact that in 4 of these cases the urinary estrogen rose to levels comparable with other cases in which the follicle-stimulating hormone disappeared. In one case more than 50 R.U. of follicle-stimulating hormone per liter persisted in the urine eighteen weeks after the institution of pellet therapy, even though the urinary estrogen output was 15.5 R.U. in twenty-four hours at the same time. In another case, in which the urinary follicle-stimulating hormone was consistently below 25 R.U. per liter during two months of preliminary observations, the urinary follicle-stimulating hormone rose to 50 R.U. per liter within two weeks following the implantation of 22.0 mg. of theelin in six pellets. During the same period the urinary estrogen had risen from less than 2.0 R.U. to more than 6.6 R.U. per twenty-four hours.

3. *Effect on the Vaginal Mucosa.*—In 10 cases biopsies of the vagina were taken before treatment, and in every case the mucosa was atrophic with a thin layer of stratified squamous epithelium. Following pellet therapy the vaginal mucosa uniformly showed increased growth with thickening of the squamous layer and mitotic figures in the basal layers. In most cases this growth activity has become evident within the first two weeks after treatment though in one case the mucosa was still atrophic in three and one-half weeks, but became proliferative within four weeks after a second implantation of pellets and has continued so for eleven weeks. In another case vaginal biopsy still shows proliferative mucosa twenty-one and one-half weeks after the beginning of pellet therapy. These cases, also, are still being studied.

4. *Effect on Subjective Symptoms.*—All patients have reported improvement, but the degree and duration of relief of symptoms have been variable. Eighteen of 21 patients have considered themselves to be relatively symptom free for periods varying from two to fourteen and one-half weeks after a single treatment. In every case the return of symptoms has been gradual, and a second implantation has again allayed the symptoms. In 3 cases the symptoms were considered by the patients to be improved only. In one of these cases, however, the number of hot flushes has been reduced from 8 to 3 per day, and this relief has continued for sixteen weeks following treatment.

The correlation between subjective symptoms, urinary estrogen levels, urinary follicle-stimulating hormone levels, and condition of the vaginal mucosa, has not been entirely uniform. In general the patients who have reported the most marked and prolonged symptomatic relief, have also had the most marked increase in urinary estrogen level and have had less than 25 R.U. follicle-stimulating hormone per liter remaining in the urine. On the other hand, in some cases the symptoms have begun to recur when the urinary estrogen level was still at its peak, and when the vaginal mucosa was still proliferative. Patients whose urinary follicle-stimulating hormone level has remained above 25 R.U. per liter have had only brief or partial relief of symptoms.

*Remarks on the Use of Subcutaneous Pellets.*—We have done 40 subcutaneous implantations of estrogenic pellets in 21 patients, and in no instance has there been infection, inflammation, pain, tenderness, or other unpleasant reaction at the site of implantation. With pellet therapy we have encountered no instance of uterine bleeding such as is sometimes seen after large doses of estrogens in oil. In no case have there been any detectable breast changes following pellet implantation.

#### DISCUSSION

In this preliminary series of 21 cases we have been able, by means of a simple subcutaneous implantation of compressed pellets of crystalline

from 2 to 24 months. Those with oligomenorrhea had a scanty flow throughout the period, which usually lasted one day.

Fourteen of this group were treated with emmenin, 4 were supplemented with anterior pituitary-like hormone, while 5 others received anterior pituitary-like hormone only.

The 14 women treated with emmenin above improved symptomatically. Periodicity was re-established in those with an amenorrhea of four months or less. In 85.7 per cent of these patients the correction was permanent. One of these, with a four months' amenorrhea, became pregnant. Failure to menstruate was universal in those having amenorrhea of six or more months. One girl, with an amenorrhea of six months and almost nightly "convulsive" seizures, was reduced to one in two or three weeks, but menstruation did not appear.

In those treated for oligomenorrhea, the periods were lengthened from one to three days. The amount of bleeding, however, was but slightly increased.

There were 4 cases in which emmenin was complemented by anterior pituitary-like hormone.

CASE 1.—Patient, 38 years old, had an amenorrhea of twenty-four months. Her periods were regular up to six months after marriage. Thereafter the interval lengthened. She was placed on emmenin for one month. No change occurred objectively or subjectively. The medication was changed to anterior pituitary-like hormone. She developed a sense of well being and "felt fine," much more so than when on emmenin, but no menstrual molimen, menstruation, or menopausal symptoms appeared.

CASE 2.—Patient, 22 years old, had scanty periods, one day in duration, recurring about every 40 days, and associated with dysmenorrhea. She was placed on emmenin. One month later she menstruated one and one-half days and again four weeks later for only one day. The medication was changed to anterior pituitary-like hormone. Menstruation recurred every four weeks and lasted four days. Five months later she became pregnant.

CASE 3.—Patient, 39 years old, had an amenorrhea three months; headaches. After one week of emmenin she menstruated and the headaches ceased. When she discontinued the emmenin the periods would likewise stop. Five months later she was placed on anterior pituitary-like hormone. The interval between periods was increased to five weeks. Emmenin was given again.

CASE 4.—Patient, 25 years old, had an amenorrhea of seventeen months following a curettage. She was placed on emmenin and felt well but did not flow. She was given anterior pituitary-like hormone and she developed hot flushes, with dysmenorrheic pains associated with a monthly menstrual molimen, but no bleeding. All symptom complaints were controlled with emmenin.

Of the 5 who received anterior pituitary-like hormone only, 2 discontinued treatment. The other 3 showed definite improvement.

CASE 1.—Patient, 19 years old, had an amenorrhea for three months. She passed clots with her periods or had nosebleeds and headaches. She received an incomplete series of anterior pituitary-like hormone (14 c.c.). Headaches were aggravated; she developed visual disturbances, puffiness of face, and abdominal discomfort. With the discontinuance of this treatment all these symptom complaints disappeared. Surprisingly enough, normal menstruation was established.

CASE 2.—Patient, 21 years of age, had an amenorrhea for eight months. After 7 injections she showed a strong female sex hormone reaction and developed periodic menstrual molimen without bleeding.

CASE 3.—Patient, 23 years old, had an amenorrhea of four months. After 8 injections, monthly periodicity of a "good flow, best in months" was established and with the exception of a two-month interval, she has since menstruated regularly.

# THE TREATMENT OF ABNORMAL MENSTRUAL FUNCTION WITH ESTROGENIC AND GONADOTROPIC HORMONES\*

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THE following report is based on a clinical evaluation of the effectiveness of estrogenic and gonadotropic hormones in patients with menstrual derangements.

The estrogenic hormone used was an active oral preparation known as emmenin. The gonadotropic hormone used was anterior pituitary-like substance. These preparations are derived from the human placenta by differential solubility. The estrogenic hormone, emmenin, is standardized so that one teaspoonful contains 120 day-oral (Collip) units. The gonadotropic hormone, A.P.L. or anterior pituitary-like, is at present standardized at 500 Collip rat units per c.c. At the time of beginning this study, each c.c. contained 100 units.

## THERAPY AND DOSAGE

As a rule, one teaspoonful of emmenin in a glass of water was given three times daily. The contents of the glass were not drained at once, but sipped over a period of hours, in the hope that the estrogenic hormone could be concentrated more or less constantly in the circulation. Both the stock bottle of emmenin and the diluted emmenin were kept in the refrigerator.

Treatment with anterior pituitary-like hormone included a period of twenty-eight days. A series of 18 intramuscular injections of 1 c.c. each was given, the first seven on consecutive days, and the next eleven on alternate days. Since the strength of the anterior pituitary-like hormone has been raised to 500 Collip rat units per c.c., we have administered  $\frac{1}{2}$  c.c., containing 250 Collip units, at each dose.

Ninety-eight patients were treated and followed for three or more years. They were divided into two major groups:

1. Estrogenic dysfunction (71 patients), included oligomenorrhea, amenorrhea, dysmenorrhea, and menopause.
2. Gonadotropic dysfunction (27 patients), included those in whom the primary complaint was menorrhagia and metrorrhagia.

## ESTROGENIC DYSFUNCTION

*Oligomenorrhea and Amenorrhea.*—(23 cases.) The criteria for classification in this group are:

1. A woman in the childbearing age.
2. Scanty or no menstrual periods.
3. The presence of grossly normal uterus and adnexa.

Often associated with these factors were, in order of their frequency, headache, dull lower abdominal pain, dysmenorrhea, and nosebleeds. The ages of the 23 in this group ranged from 17 to 42 years. The duration of the amenorrhea was

\*The emmenin and anterior pituitary-like hormone were supplied by Ayerst, McKenna and Harrison.



*Spontaneous Menopause.*—Eleven of these 13 women were promptly relieved with emmenin. As little as three drams proved sufficient in one patient. In another, 49 years old, with an established amenorrhea and all the classical menopausal symptoms, the symptom complaints disappeared and her periods returned. On withdrawal of the hormone, the amenorrhea and all the associated menopausal symptoms reappeared. She was kept under observation for two years.

In two, all the symptom complaints were aggravated. One developed a choking sensation with precordial pains which disappeared with discontinuance of treatment.

Of the two with unilateral ovaries, one improved while on emmenin, while the other was aggravated.

*Comment.*—The menopause with its associated vegetative imbalance is a fertile field for the successful administration of the estrogenic hormone. However, it seems that a more favorable response can be obtained in the presence of ovarian tissue. Relief from the symptom complaints is prompt, usually lasts for long periods and can be maintained by subsequent occasional doses. The effectiveness of oral administration of an active estrogenic hormone preparation contributes much to the ease of maintaining these patients under treatment.

### GONADOTROPIC DYSFUNCTION

All patients presenting menorrhagia and metrorrhagia as the chief complaints, and in whom the pelvis was free of any apparent inflammatory or organic change, were classified under this head. Lumbosacral backache, headache, and mastodynia were prominent among the associated symptom complaints.

Twenty-four of the 27 women in this group were followed from one to three years. All received anterior pituitary-like hormone, in divided doses of 1 c.c. (100 Collip day units) daily for seven consecutive days, and 1 c.c. on alternating days for 11 more injections. The entire course included twenty-eight days. Two of these women had emmenin as well.

The immediate reaction, that is, control of the amount of blood loss and amelioration of the symptoms, was favorable in 22 of the 25, or 88 per cent. There were two failures. One 28-year-old patient, who had had a left salpingectomy and a right cystectomy and myomectomy, had no relief after 28 c.c. (2,800 day units) of anterior pituitary-like hormone. A dilatation and curettage was done four months after treatment was started. Curettings showed an early premenstrual phase. The periods continued to be profuse and lasted eight days.

The other patient who was 32 years old, with a history of thirteen days of profuse bleeding in each of the previous seven months, responded to the first course of anterior pituitary-like hormone. The menstrual period was reduced to six days. After three months of further treatment she reverted to her former cycle.

As mentioned above, there were two who in addition to anterior pituitary-like hormone received emmenin. One, 23 years old, complaining of dizziness, headache, weakness, and hot flushes at times, had been staining daily for two years. She was placed on emmenin. There was prompt improvement. The intermenstrual bleeding stopped and all her symptom complaints were relieved. However, when the emmenin was discontinued the metrorrhagia, that is, the daily scanty spotting, returned. Again she was given emmenin. This time the bleeding became profuse. Anterior pituitary-like hormone therapy was promptly instituted. After 15 c.c. of one hundred day units each, the amount of bleeding was decreased and after three additional injections of 200 day units each, all bleeding ceased. Her subsequent periods were regular, of four days' duration and moderate in amount.

The second patient was 21 years old. She menstruated profusely every two months, each period lasting seven days, being accompanied by large clots. In addition to painful breasts and a basal metabolic rate of plus 5, she had a mild hypertrichosis. After 10 injections of 100 Collip day units each, the next three periods occurred monthly, without clots, moderate in amount, and lasted only four days. Thereafter she ceased menstruating. The estrogenic hormone, emmenin, was given. After two and one-half months of daily emmenin, hot flushes appeared.

Two other patients followed a somewhat similar course.

*Comment.*—Recent temporary loss of menstrual function is apparently chiefly due to deficiency of the estrogenic hormone. The oral administration of an active preparation of this hormone is effective in overcoming this deficiency, thereby restoring normal menstruation. In a minority of patients the anterior pituitary fails sufficiently to stimulate estrogenic function of the ovaries. In these patients, the administration of the anterior pituitary hormone alone or in conjunction with the estrogenic hormone is effective.

#### DYSMENORRHEA

There were 17 patients in whom premenstrual, menstrual, or postmenstrual pain was the dominant symptom complaint. Twelve of these were divided into two groups.

A. Those with a diminished menstrual blood loss received emmenin daily for one month, which was repeated if necessary.

B. Those with an increased menstrual blood loss were given a course of anterior pituitary-like hormone injections.

There was a third group in whom the hormones were alternated.

Six in Group A responded favorably but only one was permanently relieved. Likewise, all who received anterior pituitary-like hormone because of the associated menorrhagia were promptly improved. One of these patients became pregnant. As in the emmenin treated group, only one was permanently relieved of pain.

In two, the treatment was alternated between emmenin and anterior pituitary-like hormone. One of these did remarkably well on anterior pituitary-like hormone. The pain and amount of flow were definitely diminished and the associated nervousness and emotional disturbances lessened. The other did as well on anterior pituitary-like hormone as on emmenin. Both of these women required continued treatment for a long time to maintain painless periods. With cessation of treatment, the dysmenorrhea promptly returned.

For dysmenorrhic women with diminished flow, emmenin was satisfactory, although temporary; the longest period of relief without continuous treatment being two months. Those in whom the menstrual flow was increased responded favorably to anterior pituitary-like hormone. Unfortunately, in our hands permanent relief was not the rule. However, freedom from discomfort lasted for as long as six months.

*Comment.*—The hormonal disturbance associated with or causing dysmenorrhea is apparently not always of the same nature. The relief of the pain seems to depend upon supplying the deficient hormone. The results obtained are almost invariably of a temporary nature.

#### MENOPAUSE

Thirty-one women were treated with emmenin for symptoms ascribable to menopause. All had an amenorrhea of from two months to twelve years. Hot flushes, followed in order of their frequency by headache and dizziness, nervousness, emotional instability, and chilly sensations were the most prominent symptom complaints. Eleven had an artificially produced menopause. Twenty-five were followed from one to two years. These were divided into:

##### A. Induced Menopause (12)

Hysterectomy with bilateral salpingo-oophorectomy	6
Hysterectomy with unilateral oophorectomy	3
Hysterectomy with retention of adnexa	1
Hysterectomy with radiation	1
Radiation	1

##### B. Spontaneous Menopause (13)

Unilateral salpingo-oophorectomy	2
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*Artificial Menopause.*—Of the 6 who had hysterectomy with bilateral salpingo-oophorectomy, 2 were made worse and 3 were definitely improved by emmenin. One of the latter developed periodic menstrual menses. All with retained ovaries improved and remained so after two months' treatment. The patient treated with radium was finally relieved by emmenin.

## INTESTINAL OBSTRUCTION AS SEQUEL TO THE WEBSTER-BALDY OPERATION FOR UTERINE RETROVERSION

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IT IS valuable at times to call attention to certain inherent dangers that may follow fairly simple operative procedures. One such danger exists in the performance of the Webster-Baldy operation for retroversion of the uterus. This operation was first described by Webster<sup>6</sup> in 1901 and later by Baldy<sup>2</sup> in 1903. In 1915 Webster<sup>7</sup> again wrote concerning his operation reviewing the technique, and for reasons not disclosed warned that the openings made in the broad ligament during the course of the operation should be closed carefully so that there would be no aperture remaining through which hernia could develop.

### REVIEW OF LITERATURE

In 1920 Richardson<sup>5</sup> reported a case of intestinal obstruction following the Webster-Baldy operation which had been done two years previously. The patient was 42 years of age. A loop of ileum was found herniated through an aperture in the right broad ligament. The perforation of the broad ligament was external to the round ligament which also passed through the opening. There was no aperture in the left broad ligament. Richardson believed that the round ligament on the right side was drawn through the broad ligament which may have been thin and too far away from the body of the uterus and possibly that too large an opening may have been made. He thought that these factors would tend to make the round ligament cut through the broad ligament toward the body of the uterus and median line. This tendency, he felt, would be increased by a recurrence of the retroversion, thus an opening or a perforation of considerable size might form. He assumed that the operation was done correctly and that the opening made in the broad ligament at the time of operation was properly closed.

In 1929 Pemberton and Sager<sup>4</sup> reported a case in a female, aged 39 years, of intestinal obstruction twenty-four days after a Webster-Baldy suspension had been done. The edges of the openings which were made in the broad ligament had not been sutured, thus leaving an aperture through which a loop of small intestine two meters in length had passed. In the same report they described a case of a female, aged 36 years, who was operated for uterine fibroids upon whom a Webster-Baldy operation had been done twelve years previously. At the time that she was operated upon for her fibroids, there was a large opening in each broad ligament at the point where the round ligament perforated the broad ligament. These openings were large enough to admit two fingers. There was no intestine in either of the openings.

Arnold<sup>1</sup> in 1938 reported a case of intestinal obstruction nine years following a Webster-Baldy suspension operation of a female, aged 34 years. Two years following the suspension she was delivered of a full-term child. About nine months after the child was born she had the first attack which might be considered as being due to herniation through an opening in the broad ligament. Following this she had about two attacks a year until about nine years after her operation, at which time she had an attack of intestinal obstruction for which she was operated upon and a loop of intestine was found incarcerated in the aperture in the broad ligament.

The first of these was 36 years old, with a history of menorrhagia and metrorrhagia with clots. In December, 1935, she was placed on anterior pituitary-like hormone. There was prompt improvement. The menorrhagia and metrorrhagia were replaced by regular, periodic menstrual periods, moderate in amount and without clots. This continued until September, 1936, or about nine months. At this time she was admitted to a state hospital for a mental disorder. Her periods ceased. The amenorrhea was still present one year later.

The last of this group was an unmarried girl, 26 years old, who came to us in May, 1935, complaining of severe menorrhagia and metrorrhagia, associated with weakness and headache. Basal metabolic rate was plus 6. After 32 c.c. of 100 Collip day units in each cubic centimeter had been administered in divided doses, bleeding was finally controlled in August, 1935. Thereafter menstruation recurred every three weeks, just a small amount for one day. This continued for nine months, until May, 1936, when she skipped one period and thereafter the flow gradually increased until the bleeding again became profuse. Additional anterior pituitary-like hormone had no effect. In March, 1937, or about 10 months later, we were informed that after a course of 10 to 12 x-ray treatments, all bleeding ceased. She then developed a psychosis with suicidal tendencies and had to be committed to a state institution.

In the rest of this group, a single course of anterior pituitary-like hormone therapy as outlined above, was sufficient to ameliorate all symptom complaints, such as profuse and prolonged menstruation, intermenstrual bleeding, headaches, dizziness, and breast pains.

*Comment.*—It appears that anterior pituitary-like hormone in proper dosage is effective in regulating irregular or profuse menstruation. In some patients this action may be carried too far and as a result, oligo- or amenorrhea may occur.

#### DISCUSSION AND SUMMARY

The type of menstrual dysfunction may clinically indicate the responsible hormonal deficiency. This can be used as a basis for therapy. In our series of cases the majority with deficient or absent menstrual bleeding responded favorably to the oral administration of an active and potent estrogenic hormone.

This was accomplished by supplying a stimulus lacking in these patients. That the estrogenic hormone was not always missing, is shown by those patients who responded to the administration of the gonadotropic hormone.

In those with excessive or irregular menstruation, good results were obtained by the use of the gonadotropic hormone. It is, however, necessary to be cautious in its administration, lest an overaction occur and a "hyperluteinization" be established.

The results in dysmenorrhea, using the indicated hormone, are almost invariably of a temporary nature.

The condition which responds most readily to hormonal therapy is that produced by a lack of estrogenic hormone resulting in menopausal symptoms. The response appears to be better in those who have some ovarian tissue.

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## DISCUSSION

There are a number of reasons for which openings may be found in the broad ligament following Webster-Baldy operation. The first and most important would be the failure to close the aperture made at the time of the operation. This was thought to account for the case reported by Pemberton and Sager<sup>4</sup> and must have been present in Webster's mind as a potential source of danger when he wrote his second article. A second reason could be a recurrence of the retroversion accompanied by pulling on the round ligaments, causing them to separate from the area where they have been attached to the broad ligament. A third reason could be due to growth of the uterus by tumor or pregnancy which would cause undue tension on the round ligament, thus tending to tear the broad ligament at the site of the previous operation.

The case reported herein, the case of Parkes and Karabin, and the case of Arnold were known to have had one or more pregnancies between the time of suspension and the time of the intestinal obstruction. None of the cases that had obstruction were accompanied by tumors of the uterus. However, Pemberton and Sager described a case in which openings were found in both broad ligaments but without any herniation.

It would seem that the Webster-Baldy operation, although simple of technique and a safe operation in careful hands, even when properly done, is not without its dangers in subsequent years, especially if pregnancy supervenes or if a tumor of any size forms in the uterus.

## SUMMARY AND CONCLUSION

Including the case herein reported there are reports of 6 cases of intestinal obstruction due to herniation through an aperture in the broad ligament, occurring from twenty-four days to nineteen years following a Webster-Baldy operation. There is one case in which apertures were present without herniation.

In cases of suspected intestinal obstruction where previous operation has been done, it would be well to inquire from the patient whether the operation was for suspension of the uterus, and, if so, this should be kept in mind by the surgeon in order to govern the technical approach.

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Parkes and Karabin<sup>3</sup> in 1939 reported a case of intestinal obstruction following a Webster-Baldy suspension operation which had been done fifteen years previously. No mention was made whether any pregnancy had occurred in the interim. A footnote in the same article stated that one of the authors (J. E. K.) participated in another case of intestinal obstruction in which a Webster-Baldy operation had been done ten years previously. This patient had two full-term pregnancies in the interim.

#### CASE REPORT

The case herein reported was that of a patient, aged 44 years, who had an operation for suspension of the uterus nineteen years previously. Following the operation three full-term pregnancies occurred. As long as twelve years ago or seven years following the suspension operation she complained of pains and tenderness in the lower abdomen and was told by a doctor that there was a tumor in the rectum. A later examination revealed no tumor and her trouble disappeared.

She entered the hospital Nov. 4, 1938, complaining of gaseous distention, obstipation, nausea, and vomiting. She stated that she was well until October 24 when she began having abdominal pains and cramps which were later generalizing throughout the abdomen and becoming associated with nausea, vomiting, and abdominal distention. There were intervening periods which lasted from two to three hours in which the pain was much less severe.

On the first day of her illness she took some castor oil which caused a bowel movement. On November 1 there was a bowel movement following an enema. She stated that there was no blood in her stools on these occasions. There were no other bowel movements during her illness.

The vomiting was not related to intake of food and was not projectile. It was green in color. She was unable to take solid food following the onset. For two days she had hiccups which persisted and were troublesome.

On physical examination she was found to be acutely ill, entirely rational and cooperative. The only abnormalities of importance in the physical examination were found in the abdomen which was markedly distended and tympanitic. There was no rigidity and the only pain or tenderness elicited was on palpation of the left lower quadrant in which area a soft indefinite mass could be felt. There was noted an old healed lower abdominal surgical scar which was not tender. No fluid wave could be elicited.

At the time of admission the nonprotein nitrogen of the blood was 150 mg./100 c.c. The whole blood sodium chloride was 330 mg./100 c.c. The white blood count was 57,000; the differential contained 95 per cent polymorphonuclear cells of which 47 per cent were nonfilaments, 4 per cent lymphocytes and 1 per cent monocytes. She had a temperature of 98.4° F., a pulse of 108, and respirations of 20.

An operation was done by Dr. Frank A. Kelly soon after admission. Under spinal anesthesia, a low left rectus incision was made. Upon opening the peritoneum large distended intestines were found which were dark in color. On slight manipulation a large quantity of free pus flowed from the incision. Because of the condition of the patient, no further procedures were carried out and drainage was inserted. She died fourteen hours after the operation.

At post-mortem examination, the only findings of importance were in the abdomen. The omentum was seen to cover the viscera and was fastened by old dense adhesions in the lower left quadrant. On freeing the omentum from this area a loop of small bowel presented which was brownish red in color; accompanying this there were about 300 c.c. of foul-smelling thin yellow pus. On removal of the intestinal tract, there was found that about 45 cm. of ileum were herniated through an opening in the large left ligament, about 1 cm. inferior to the midtubal region, the hernia extending from before backward passing posteriorly through the broad ligament into the cul-de-sac. This segment of ileum was strangulated, dark purple in color and had an area of perforation from which fecal material was exuding. Surrounding this mass there was a semiwalled-off abscess from which pus exuded. Further examination of the intestinal tract revealed numerous adhesions about this area and no diverticula, ulcers, or tumors. There was no opening in the right broad ligament.

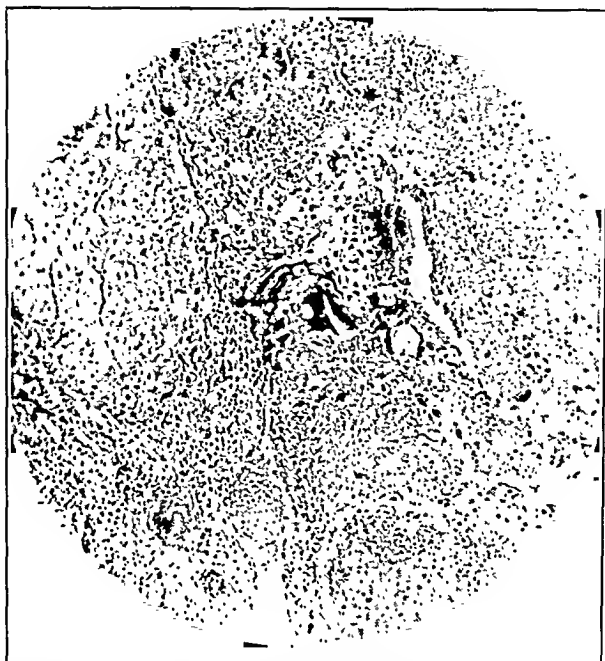


Fig. 1.—Microphotograph. ( $\times 100$ .) The pale zone on the left is composed of lutein cells. The dark areas on the right are blood clots. In the center a group of syncytial giant cells and Langhan's epithelial cells are seen. (Hematoxylin and eosin stain.)



Fig. 2.—Microphotograph. ( $\times 100$ .) This is only one microscopic field removed from Fig. 1. Some of the clot is the same as that seen in Fig. 1. Note the chorionic villi, syncytial giant cells and Langhan's epithelium. (Hematoxylin and eosin stain.)

## OVARIAN PREGNANCY

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PATIENT, white, housewife, aged 20 years, gravida 0, was first seen in October, 1938, because of the complaint of sterility. The patient had been using contraceptive methods until the previous four months. The physical and pelvic findings were essentially normal. No treatment was advised at this time. She was next seen in her home on the evening of March 19, 1939, complaining of lower abdominal pain which was more severe in the right lower quadrant.

Menses began at the age of 12 and occurred regularly every twenty-eight days, lasting three days without pain. She gave a history of the usual childhood diseases, good general health and no previous surgery. Her last normal menstrual period occurred on Jan. 8, 1939. Her next period was on February 5, and lasted five days but the flow was intermittent. On March 5, the menstruation consisted only of a pink vaginal discharge which has continued daily since that time.

On March 16, as she sat down, she felt a severe knifelike lower abdominal pain more severe on the right which persisted for one-half hour. Two days later she ate a large dinner, and the nausea and vomiting which followed were attributed to the unusual food she had eaten. The following morning she had some vague cramping pains in the right lower quadrant of the abdomen associated with general abdominal soreness and a mild diarrhea. That evening a severe, knife-like pain began in the lower abdomen, somewhat more severe on the right, and not radiating to the back or thigh. Examination at this time did not reveal any pallor. The pulse rate was 88; the blood pressure was 120 systolic and 80 diastolic. The heart and lungs were normal. The abdomen was not distended, but there were moderately severe tenderness over the lower abdomen and considerable muscle guarding. The uterus apparently was normal in size and position. The pelvic examination was unsatisfactory because of tenderness which seemed to be more marked in the right adnexal region where a small, extremely tender mass was felt and thought to be the right ovary. The diagnosis of an ovarian cyst or of a tubal pregnancy was considered and the patient was advised to remain in bed for further observation.

One hour later the husband reported by telephone that his wife had fainted. Her blood pressure was 100 systolic over 80 diastolic, pulse 100, and temperature 100° F., just before she was sent to the hospital. There was no shoulder pain.

A catheterized specimen of urine showed nothing unusual. The hemoglobin was 79 per cent Sahli (17 gm. in 100 c.c.), and the white blood cell count was 14,500 per c. mm. with 82 per cent polymorphonuclears. Under anesthesia, bimanual pelvic examination revealed a 4 or 5 cm. doughy mass in the right adnexal region. Bright red blood was obtained on cul-de-sac puncture.

Upon opening the peritoneum, approximately 500 c.c. of mixed fresh and old blood were found. The uterus was normal in size and position. Both tubes and the left ovary were carefully examined and found to be normal. One pole of the right ovary contained a yellow tumor mass, 3 cm. in diameter, bleeding freely around a blood clot about 5 cm. in diameter. This mass was interpreted as a bleeding corpus luteum. The left Fallopian tube was not in contact with any portion of the blood clot. A wedge-shaped incision was made in the ovary and the yellow body peeled from its bed. The cut surfaces of the ovary were closed with interrupted mattress sutures of fine catgut. A portion of the blood clot was separated from the corpus luteum during its removal.

The patient recovered uneventfully and was discharged from the hospital on the twelfth postoperative day.



## TREATMENT OF CERVICITIS DURING PREGNANCY\*

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CINCINNATI, OHIO

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THE pregnant woman with a marked cervicitis and profuse leucorrhea presents a definite problem. Because of the generally increased sensitivity of the pregnant state she suffers with particular acuteness. Furthermore, although the correlation between cervicitis and puerperal infection has never been proved, it would seem theoretically that an infected cervix is a potential source of danger at the time of delivery. Yet, because of the gravid condition, there is a tendency to avoid any type of treatment.

Most of the textbooks specifically interdict any manipulation of the cervix during pregnancy because of the danger of inducing abortion or premature labor. This prohibition has extended in some clinics even to the insertion of a bivalve speculum. With the development of better technique, however, has come the feeling that the dangers are more theoretical than real, and within recent years, the amount of treatment permitted has gradually been increased.

Of the many methods of treating cervicitis in general, the actual cautery has proved among the most successful. It is undoubtedly more drastic than topical applications or caustic chemicals, but is, in careful hands and with due regard to conditions, perfectly safe.

A survey of the literature reveals the warning in almost every paper dealing with cauterization of the cervix that pregnancy is a contraindication, but none of the authors reports any data to support the statement. On the other hand, in 1931 Miller, Martinez, and Hodgdon<sup>1</sup> reported a series of 2,000 women in whom the cervix was cauterized antenatally. There was only one abortion, a percentage far lower than seen ordinarily in 2,000 pregnancies. Castallo and Montgomery<sup>2</sup> in 1935 stated that the cervix may be treated antenatally without danger to the mother or the embryo. In Goldblatt's<sup>3</sup> series of conization of the cervix, there happened to be 20 women pregnant from one to nine months, not one of whom went into premature labor or aborted. The evidence, therefore, seems to indicate that the dangers of treating the gravid cervix, even by so formidable a method as cauterization, are largely exaggerated.

The experiment reported here was undertaken in an effort to treat leucorrhea, due to nongonorrheal cervicitis, in pregnant women. The criteria for treatment were complaints of leucorrhea and the finding of either erosion or an old laceration or both. Gonorrheal cases were not treated. The cases were otherwise unselected and the data concerning the delivery were obtained from independent observers at the hospital. The treatment was given at one sitting, between the twentieth and thirtieth weeks of pregnancy, and consisted of fairly deep linear cauterizations on both lips of the cervix in more or less radial fashion, but including the lateral margins of the os where laceration was present. No

\*Read at a meeting of the Cincinnati Obstetrical Society, December 21, 1939.

The following pathologic report is by E. M. Hall, M.D.

*Gross Examination.*—"The specimen consists of two separate pieces of tissue: (1) a hemorrhagic nodule of soft tissue which measures 2 by 2 by 1.5 cm. This has been opened and in the center there is a pale membranous cystlike structure, apparently the amniotic sac of an ectopic pregnancy. The embryo cannot be distinguished. The narrower irregular base of this mass matches exactly ringlike areas on piece No. 2; (2) a yellowish nodule, 2 cm. in diameter, oval in form, and slightly cystic in the center. Within the thin capsule there is a zone of bright yellow tissue about 3 mm. in thickness. The base is irregular where the mass (corpus luteum) has been removed from the ovary. On the smooth, rounded, outer surface there is a roughened circular hemorrhagic area where the first piece has been attached."

*Microscopic Examination.*—"Sections through (1) the hemorrhagic mass, show a broad zone composed of large, pale-staining lutein cells. There are many small, rounded, clear spaces in the cytoplasm of these cells where the lipoid has dissolved out.

"The main part of the section consists of a blood clot to which a portion of the corpus luteum is attached. Between the masses of clot are numerous chorionic villi, syncytial giant cells, and groups of Langhan's epithelial cells showing vacuolated cytoplasm (Figs. 1 and 2).

"Sections through (2) the corpus luteum, show a thin layer of ovarian tissue about the outside, forming a sort of capsule. The broad zone of lutein cells is 3 or 4 mm. in thickness. Unluteined granulosa cells are seen toward the outer border and also in the form of wedgelike masses extending for some depth into the luteinized zone. Red blood cells, fibrin, and partly organized clot are seen within the central cystic part."

*Diagnosis.*—"Ovarian pregnancy."

#### DISCUSSION

In this case as in the one reported by Thro,<sup>4</sup> chorionic villi were found embedded both in the corpus luteum and in the surrounding blood clot. The embryo was not found. Although we do not have microscopic sections of the Fallopian tubes to prove the absence of any pathologic changes, we feel justified in concluding that the findings are those of a primary ovarian pregnancy.

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Zelic, M.: Bleeding From a Pregnancy Corpus Luteum as an Indication for Laparotomy, Zentralbl. f. Gynäk. 62: 989, 1938.

The literature in regard to ovulation bleeding, corpus luteum bleeding, and something of traumatic ovarian bleeding is briefly summarized. A case history is presented. A 23-year-old patient had had two normal pregnancies and three spontaneous abortions. The last menstrual period was seven days later than expected. After a forty-one-day period of amenorrhea, there was sudden pelvic pain, vomiting, and loss of consciousness. The patient was admitted with evidence of severe anemia and in shock. Operation showed 1,000 c.c. of blood in the peritoneal cavity. Bleeding was occurring from a corpus luteum in the left ovary which was removed. Careful examination of this showed no other abnormality than the source of the hemorrhage. Eight days later uterine bleeding began and an apparently normal three months' pregnancy was removed. The patient was discharged well.

The cause of the corpus luteum hemorrhage is ascribed to psychic disturbances.

J. L. McKELVEY.

# ECTOPIC PREGNANCY COMPLICATED BY UTERINE FIBROID

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NOTWITHSTANDING years of research, no definite single reason may yet be given for the abnormal implantations in the tubes of ova. Changes in the anatomy and physiology of the tube or of the ovum, acute and chronic salpingitis, present or previous inflammations, swellings of the tubal mucosa, and obstruction by tumor growths have been presented as possible, perhaps probable, factors.

Operation in the early stages of ectopic pregnancy frequently reveals no evidence of previous inflammation. Here other factors are to be considered, perhaps related to the ovum or to some other impediment to its normal passage. In this connection tumors have often been regarded as favoring the development of ectopic gestation. In the present case, a large fibroid offered a real obstacle to the ovum, and caused its probable nidation in the tube.

Mrs. E. R., aged 37 years, complained of abnormal bleeding over a period of eight weeks. She had been well throughout her life, had had a normal menstrual history from the age of 13, had been married at 22, and had had one child three years later. Her menstrual periods had been regular and of five days' duration until eight weeks before her appearance at my office. At that time she had begun to menstruate and the flow had continued for almost three weeks, with interruptions. No pain or discomfort had been associated with the bleeding. For a week she had been symptom free, and then the bleeding had been resumed, continuing intermittently until she reported for examination.

The patient was a well-developed woman, 5 feet 6 inches tall and weighing 122 pounds. Temperature and pulse rate were normal. The only significant finding was a large tumor of the uterus which almost completely filled the lower pelvis. The ovaries and tubes could not be palpated because of the size of the growth. The mucosa of the cervix and vagina was clear, colposcopy showed no sign of malignancy. There was a slight bloody flow from the cervix.

The tumor appeared to be a typical fibroid. This, in itself, could account for the bleeding, although it was puzzling to understand how so large a growth (Fig. 1) could have developed without producing symptoms at an earlier stage.

Operation was indicated, but the patient was very much opposed to such a procedure. She was therefore instructed to wait for two weeks and report for a check-up if the bleeding continued. However, after only one week had passed, the patient was forced to go to bed with severe pain. She had lifted some object in the course of her household tasks and had felt a sharp pain in the left lower abdomen. After one-half hour the pains had slightly diminished, but the abdomen in the region corresponding to the location of the left tube and ovary was tense and very sensitive.

The first impression was that torsion of the left ovary (perhaps cystic) had occurred, although the ovary could not be palpated because of the size of the fibroid. There was no vomiting; the pulse was 82, the temperature 98.8° F., and the urine normal. Urination was painless, but there was some pain after defecation. The blood count was close to normal. (Red blood count 3,900,000, white blood count 8,700, with 80 per cent polymorphonuclears, 18 per cent lymphocytes, 1 per cent eosinophiles, and 1 per cent mononuclears.) The hemoglobin was 80 per cent, and the sedimentation time, normal. Blood pressure was 130/115.

The pain had decreased somewhat and the patient was still strongly opposed to operation, so that twenty-four hours of watchful waiting were decided upon. However, no improvement occurred and the patient finally consented to surgical intervention.

Under general anesthesia, the abdomen was opened, and 100 c.c. of free blood observed in the abdominal cavity. It was obvious that we were dealing with an ectopic pregnancy as well as with a fibroid of the uterus. The tumor was difficult

anesthesia was needed. Bleeding from a pulpy cervix occurred in a few cases but did not occasion alarm and did not persist longer than a day.

### RESULTS

Including 2 cases from private practice, 48 women were treated, 13 primiparas and 35 multiparas. The records of 140 women seen concurrently in the same clinic were used for controls. Of the 48 treated patients, 2 moved away from the city and could not be located, but it is known that they were still pregnant two weeks after the treatment.

The results were gratifying. In almost one-half of the patients the leucorrhoea disappeared entirely, many of the women volunteering the information. In another one-fourth of the patients there was marked subjective improvement. The remaining few did not feel that they had been helped much. The objective evidence was even better. In all but one patient the cervix appeared healthier, usually completely cleared of erosion. Five of the women returned to the prenatal clinic with a subsequent pregnancy, and in each the cervix was smooth and healthy, suggesting a certain degree of permanence in the original cure.

The number of cases is too small to form a true statistical study, but the following comparisons were made:

1. The length of labor, as measured by averages, was about the same in the two groups. The figures were: Primiparas, treated, 16.0 hours ( $\pm 5.1$ ); controls, 17.8 hours ( $\pm 5.5$ ); multiparas, treated, 11.4 hours ( $\pm 3.6$ ); controls, 9.0 hours ( $\pm 3.6$ ).

2. Operative deliveries were proportionately fewer in the treated patients, numbering 2 out of the 46, and 15 of the 140 controls. The only cesarean section was in a control case, elective, for sterilization because of rheumatic heart disease.

3. The morbidity was about the same in both groups. Using the American College of Surgeons criteria, 4 of the 46 treated patients had significant fever (8.7 per cent) and 12 of the 140 controls (8.6 per cent). The only death was in the control group, a post-partum eclampsia following premature delivery.

### SUMMARY

1. Cervicitis and its attendant leucorrhoea are a real problem in pregnancy, because of the greater discomfort and because of the traditional fear of premature labor if any therapeutic measure, even a douche is used.

2. The absence of evidence in the literature suggests that the dangers of treating the gravid cervix are exaggerated.

3. In the experiment reported, the actual cautery was used to cure the nongonorrheal cervicitis of 48 women between the twentieth and thirtieth weeks of pregnancy. The results, both subjectively and objectively, were good.

4. There was no premature induction of labor, and comparison with 140 controls revealed no significant change in the length of labor, the incidence of operative delivery, or the morbidity. Since the cauterizations were done on the diseased cervix and the control cases were relatively healthy, these data seem to be favorable for the treated cases.

5. While the actual cautery is not to be recommended routinely or to untrained individuals, it appears that cervicitis during pregnancy may be treated successfully and safely.

Appreciation is expressed to Dr. Carl A. Wilzbach, Health Commissioner, Dr. F. Kirby Harder, Assistant Health Commissioner, and Dr. H. L. Woodward, director of the Obstetrical Service of the Cincinnati General Hospital, for their cooperation.

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# ACTINOMYCOSIS OF THE INTERNAL FEMALE GENITALIA

## WITH REPORT OF CASE

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**A**CTINOMYCOSIS of the internal female genitalia is a rare disease. Up until 1934, when Cornell reviewed the world literature, only 71 cases had been recorded. Since then several cases have been reported both in this country and abroad, but the number on record is still small.

Actinomycosis may be defined as a chronic infection caused by the *actinomyces bovis*, or ray fungus, and is characterized by the formation of multiple abscesses which discharge an exudate containing colonies of characteristic yellow granules.

We wish to report another case of actinomycosis of the pelvic organs.

Mrs. I. W., age 54 years, was first seen at the University Hospital in January, 1938, at which time she stated that she had always been in excellent health until after her third pregnancy, following which she developed symptoms of relaxation of the pelvic floor and prolapse. At this time she was also found to have a mild diabetes mellitus. She had passed through the menopause at the age of 52, two years before admittance.

In the fall of 1936 the patient first began complaining of abdominal pain, located chiefly in the lower right quadrant. In November of 1936 she had an acute attack of pain which was diagnosed as "appendicitis." This subsided under conservative therapy, but the lower abdominal pain and discomfort persisted. In the spring of 1937 her diabetes required insulin. Shortly after this she developed a vaginal discharge which she was told was due to an infection in her tubes. Later in 1937 all of her abdominal discomfort increased, the discharge became worse, the appetite decreased, and she lost 10 or 15 pounds in weight. At this time she revealed a daily febrile reaction up to 100° F., which continued until her admittance to the University Hospital in January, 1938.

Examination at the time of admittance showed a relaxation of the pelvic floor with a second degree prolapse. The uterus was slightly enlarged and limited in mobility. There was definite thickening and induration in the posterior cul-de-sac and in the left adnexal region, with a sensation of an indefinite mass in this area. It was felt she had either a pelvic neoplasm or more likely an extensive chronic pelvic inflammatory process.

After a period of study the patient was sent home to rest and carry on conservative treatment in the form of prolonged hot douches. She returned to the hospital again in March, 1938, stating that all of her symptoms had persisted and that her diabetes had been very difficult to control. Laparotomy was advised and performed on March 27, 1938. The uterus and adnexa were firmly bound down in a mass of adhesions. A bilateral salpingo-oophorectomy and subtotal hysterectomy were done with wide removal of the inflammatory process. On examination of the specimen, the uterine wall was found to be greatly thickened and replaced in areas by soft, necrotic, gray and yellow tissue, the whole mass exuding pus on pressure. Microscopic examination of the tissue revealed an extensive actinomycotic infection of all tissue, a severe purulent inflammation throughout and sinus tracts and abscesses containing numerous colonies of actinomycetes.

Postoperatively the patient did well with no further treatment. After removal of the abdominal drain the wound continued to discharge a moderate amount of purulent material which showed no actinomyces. The wound infection appeared to be superficial with no sinuses, and had almost entirely closed up at the time of her discharge home. The patient was afebrile for several days before her release from the hospital, and her diabetes was now easily controlled.

In general, the prognosis in pelvic actinomycosis appears to be very bad. Doubtless this is partly due to the fact that most patients are far advanced before treat-

to dislodge as it was deeply enveloped with the lower part of the cervix and of the corpus. The right tube and ovary were normal and were left untouched. The left tube was a sausage-shaped mass with a blood clot passing through the fimbriated extremity (a tubal abortion). The tube had not ruptured. Hysterectomy and left salpingo-oophorectomy were done (Fig. 1).

Convalescence was uneventful and the patient was discharged from the hospital on the tenth postoperative day.

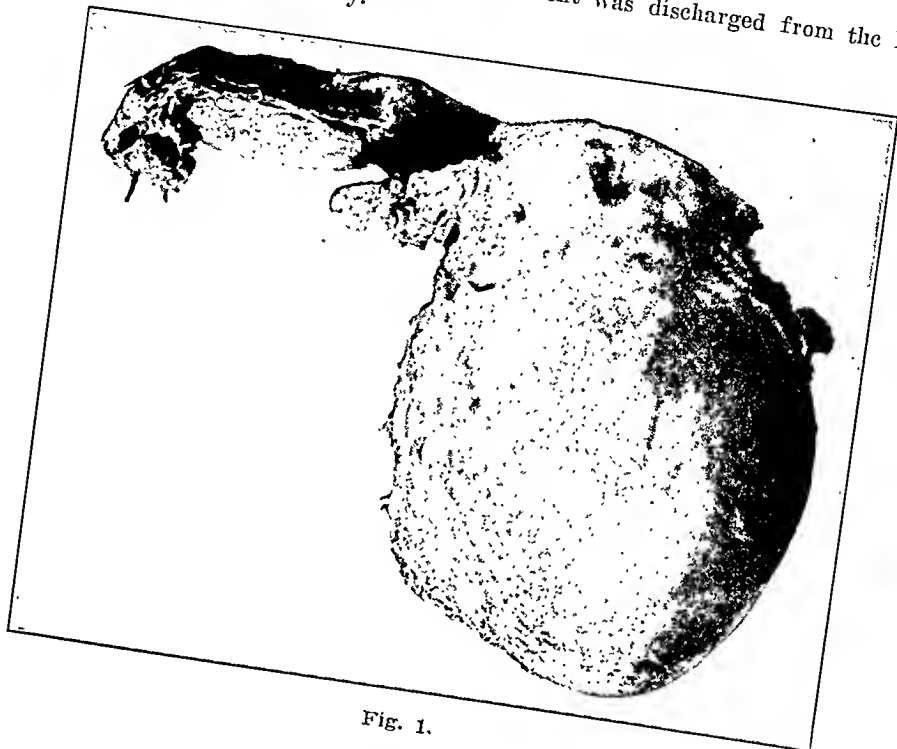


FIG. 1.

## COMMENT

This was a clear case of tubal abortion plus fibroid. Probably the tumor had so elongated and compressed the cervix and corpus of the uterus that the ovum was prevented from undergoing proper implantation.

There was little danger of fatal hemorrhage in this case since no tubal rupture had occurred, but merely a tubal abortion with rupture of the inner capsule. This could probably have healed spontaneously. Such old hematoceles are often found years later at operations for adnexal tumors or even at appendectomies.

There was no reason to suspect before operation that an ectopic pregnancy was present, since the patient had not missed a period and the abnormal bleeding could be amply accounted for by the fibroid.

11 LIVINGSTON AVENUE

structures. Further x-rays showed premature appearance of the epiphyses for the scaphoid, trapezoid, and pisiform; of the middle and proximal rows of the phalanges; of the lower end of the radius and ulna; and unduly developed sella turcica.

The spine showed excellent development of bone. The impression was one of premature osseous development throughout.

Pregnanediol determinations (Drs. Kantrowitz and Kahn) upon urine collected preoperatively, gave results comparable to those occurring in the early months of pregnancy (31 mg. of pregnanediol glucuronate).

With a preoperative diagnosis of a precocious menstruation etiologically caused by a possible granulosa cell tumor of the left ovary, the patient was laparotomized under open drop ether anesthesia on May 6, 1939 with the following findings: The uterus was regular, slightly enlarged, and of unusually soft consistency. The left



Fig. 1.

Fig. 1.—Graafian follicle with cumulus.

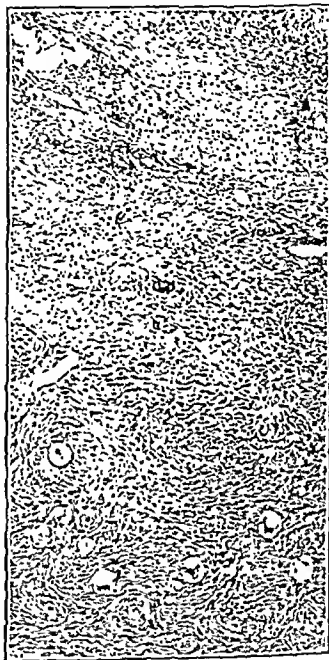


Fig. 2.

Fig. 2.—Ovary with primordial follicles.

ovary was about the size of a small plum and in appearance resembled an adult microcystic ovary. The right ovary was normal in size and appearance, solid and not cystic with a thick tunica and was about  $\frac{1}{6}$  the size of the left ovary. The tubes were grossly normal. No other abdominal masses were palpable.

*Pathologic Report.*—(No. 8821.) (Dr. A. Kantrowitz.)

*Gross:* Specimen consisted of left ovary, measuring 3.5 by 3 by 1.5 cm. and weighing 8 gm. A cystic mass, 1.2 cm. in diameter, was adherent to the midpoint of one surface of the ovary. The ovary was boggy in consistency and presented a mottled yellow and gray color with translucent areas presenting themselves beneath the capsule. The surface was smooth. Cross section revealed the presence of a considerable number of cystic areas, ranging in size from less than 0.2 cm. in diameter to a cyst measuring 1.5 cm. in diameter. All of the cysts contained clear, straw-colored fluid. The wall of the largest cyst presented a bright yellow color.

*Microscopic:* (Figs. 1 and 2.) The ovary contained no neoplasm.

There were ova in all stages of development from the primordial follicle to the mature Graafian follicle with luteinization of the theca interna. The large cyst falls into the latter category. Atretic follicles were also noted.

ment is undertaken. If this disease is borne in mind, some of the long standing, peculiar, pelvic inflammatory processes may come to surgery sufficiently early to permit adequate removal of the diseased tissues. As postoperative therapy, x-ray and iodides may be used or perhaps thymol. Under such management the ultimate prognosis may be improved.

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## PRECOCIOUS MENSTRUATION

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(From the Gynecological Service of Beth Moses Hospital)

DU E to the increased interest in the physiology and pathology of menstruation, the following case report is submitted:

R. A. (No. 87853), white, Catholic, full-term child born Nov. 22, 1934, present weight 47 pounds, and 42½ inches in height, was admitted to the Pediatric Service of Beth Moses Hospital, on April 21, 1939, with a history that her mother had noted an increased prominence of the child's breasts, nipples, and "private parts." In addition, the child had first menstruated in July, 1938, at the age of 3 years and 8 months for two days, and about every three months thereafter for two to three days. Her last menstrual period occurred during her present preoperative stay in the hospital.

The patient has one sister 6 years of age who is considered normal in every respect. Both parents were born in the United States.

Her mother's menstrual history began at the age of 15, occurring every three months, lasting for three days. However, within the past few years she has maintained a normal menstrual cycle, in that her periods have been occurring regularly every thirty days. The mother is one of 15 children, 8 sisters and 5 brothers all living and well. One brother and one sister had died of unknown causes. There was no history of any abnormality in the menstrual cycles of her 8 sisters. There was no family history of tuberculosis, cancer, or diabetes.

Mentally, the patient appeared normal for one of her own age, but physical appearance gave one the impression of observing an older individual. She was well developed, and upon physical examination was essentially negative except for markedly well-developed breasts and nipples, and markedly hypertrophied labia majora and minora. No pubic or axillary hair was noted. There were no evidences of undue muscular development or virilism.

Abdominal examination was essentially negative except for a slight fullness which was noted in the left lower quadrant. However, no tenderness, rigidity or definite masses were noted. Rectal examination revealed the presence of a freely movable mass about the size of a small plum, lying in the posterior cul-de-sac and to the left.

Ten days after admission, the patient was transferred to the Gynecological Service for further observation, study and treatment. Blood and urine were normal.

The Friedman test was negative, basal metabolic rate, plus 28 per cent, and vaginal smears were negative for gram-negative intracellular diplococcus.

X-ray studies of the abdomen showed gas presence in the colon up to splenic flexure and not below, possibly an indirect evidence of some soft tumefaction, pressing on the gut but not of sufficient density to contrast with the surrounding soft



was given two infusions of 10 per cent glucose in saline, 1,000 c.c. each. During this twenty-four-hour period, the head had advanced a little and the dilatation of the cervix was between 6 and 8 cm. The patient was surgically prepared, and under complete ether anesthesia Dührssen's incisions were made in the cervix and the baby was delivered by midforceps extraction. The baby cried spontaneously. Fourteen hours after delivery the baby had a cyanotic spell which was relieved by the removal of mucus from the throat. The following day he seemed listless at times, but he appeared to be progressing satisfactorily until the morning of the seventh day when he became very cyanotic. He was placed in an incubator and given oxygen inhalations and 2 per cent glucose solution subcutaneously. He received 40 c.c. of whole blood intramuscularly. He appeared to improve for a few hours, but again became cyanotic and died eleven hours after the first cyanotic attack.

The mother continued to have fever for seven days. She received 40 gr. of acosulfamid daily during this febrile period and 5 gr. three times a day for several days after her temperature became normal. No satisfactory explanation can be offered for the continued elevation of temperature post partum. Occasional pus cells were found in the urine at two examinations, but her condition could not be traced to this. Agglutination tests were negative. The patient had no specific complaints and did not know that her temperature was elevated until she was given this explanation for her removal from the obstetric floor. She was discharged in good condition after eighteen days in the hospital.

An autopsy was performed on the baby and the following significant findings were present:

The heart weighed 18 gm. The right auricle was markedly dilated. The epicardium was smooth and glistening and the site of occasional pin point-sized bright red markings. The myocardium was rather pale, grayish red in color. The mural endocardium was smooth and glistening; the mitral, aortic and pulmonic leaflets were thin and pliable; the tricuspid leaflets at their free margin were the site of rather indistinct and glistening excrescences not exceeding a millimeter in their maximal diameter. The ductus arteriosus was patent, thick walled, and the lining surface was wrinkled. The foramen ovale was patent, but covered with a delicate, transparent, gray membrane, which was incompletely attached to its margins.

The left lung was mottled grayish red to dark red in color and noncrepitant. The pleural surface was smooth and glistening and the cut surface was rather dark grayish red. At the lower border of the upper lobe was an 8 by 10 mm. sized area darker red than the surrounding lung and sharply demarcated on its cut surface. The right lung was smooth, glistening, and pale grayish red, except for a dorsal aspect, where it was darker red in color.

The liver weighed 100 gm. The capsule was smooth and glistening and delicately mottled dark red to purplish red and speckled with pin point, sharply circumscribed gray areas. The cut surface of the liver had a distinctly brownish cast to its dark red color and was densely speckled with pin point-sized gray to grayish tan markings.

The spleen weighed 12 gm. It was smooth, dark red, and firm. The cut surface was dark red, the markings were rather poorly defined, though here and there pin point gray markings could be distinguished.

The capsules of the kidneys stripped readily; the usual fetal lobulations were present. The surface was smooth and glistening and light red to grayish tan, with occasional bright red pin point markings. On the cut surface the cortex averaged a millimeter in thickness, the medulla was clearly demarcated, the cortical markings were rather poorly defined, the pelvis was pearly gray.

The adrenals were firm and light yellowish gray in color, heavily speckled with irregular pin point to pinhead-sized dark red markings. On the cut surface the adrenal cortex was of moderate thickness, pale yellowish gray, and speckled irregularly with dark red markings.

*Microscopic Findings.—Heart:* The muscle fibers of the myocardium of the left ventricle were well preserved; the blood vessels were not remarkable. The myocardium of the auricle was rather poorly developed and the fibrous stroma was rather edematous. The mural endocardium displayed a moderate subendocardial edema. The valve leaflets on their auricular surface were rather irregular and thrown up into low humps as a result of a rather marked interstitial edema, which achieved

*Diagnosis.*—(1) Ovary, as in puberty; (2) Graafian follicle.

The postoperative course was entirely uneventful, with the wound healing by primary union, except for the fact that as patient was about to be discharged on the fourteenth postoperative day she developed the prodromal signs and symptoms of measles necessitating her removal to the Kingston Avenue Hospital for Contagious Diseases.

Repeated follow-up examinations at about monthly intervals, have shown no very marked recession in either breasts, nipples, or vulva. Up to the time of submission of this report, approximately five months postoperatively, no further vaginal bleeding has been noted.

#### DISCUSSION AND SUMMARY

In this country with 13.9 years as the average age of onset of the menses, menstrual periods occurring and recurring regularly below the age of 9 and accompanied by some evidence of precocious maturity such as increased prominence of breasts, hair on pubis or vulva and premature skeletal development, may be definitely classified as cases of precocious menstruation.

Etiologically, one can only state that precocious puberty, like the normal process, is probably due to a stimulus arising in some way from the ductless gland chain, and especially from the generative glands. In the numerous reports of the syndrome of sexual precocity reported in the literature, the condition is ascribed by most authors to disturbances of either the pituitary body, ovaries, adrenals, or the pineal gland. Elterich<sup>1</sup> analyzing 25 cases of precocious menstruation upon whom autopsies or operations were performed, observed that in 21 of these, tumors or cysts of the ovaries were found, the majority of these tumors being sarcomas. However, neoplasms other than the granulosa cell tumors, may be the cause of sexual precocity.

Evaluating all of our presently available clinical, laboratory, and pathologic data, we do not look forward to noting a regression or recession of symptoms above described but prefer to assign this case to the first and major of the three groups described by Lenz<sup>2</sup> who collected and analyzed 130 such cases, to wit: a case of premature menstruation with evidences of general body development which characterize puberty, and not associated with any tumor involving the pineal, pituitary, ovarian or other ductless glands.

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789 ST. MARKS AVENUE

### FETAL DEATH DUE TO TOXEMIA OF THE MOTHER

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IN MANY statistical reports, listing the causes of deaths of the newborn, it is stated that toxic conditions of the mother are responsible. The literature contains no definite reports of the exact nature of this effect on the baby. We are reporting the following case because it illustrates one result of severe toxemia in the mother.

The mother, G. L., a 34-year-old white primipara, was admitted to the Augustana Hospital Dec. 20, 1938, at term. The prenatal course was essentially negative, except for a moderate amount of nausea and vomiting during the first two months of gestation. The blood pressure and urine had remained within normal limits. She had been having labor pains for approximately twenty-four hours before notifying us of her condition. On admission to the hospital she was having strong pains every three minutes. The head was in the pelvic brim and the cervix dilated about 4 cm. The temperature on admission was 98.8° F. Four hours later it was 100.2° F. and continued to rise until it reached 102.2° F., eight hours after admission. Her condition remained the same during her first twenty-four hours in the hospital. She

rate was 180 for six hours; delivery was effected by Dührssen's incisions, midforceps, and episiotomy; the baby was apparently not affected and was easily resuscitated. On the other hand, I am firmly convinced that babies are occasionally lost because of a false sense of security when the heart rate is found to be still over 100, the fact that it is becoming slower or has a tendency to become irregular not being considered significant. I feel that a slowing heart rate is a very grave matter, and that the baby is in danger. Briefly, I believe that a rapid rate means simply threatened or early asphyxia, while a slowing rate, to my mind, signifies increased intracranial pressure, and may presage intracranial hemorrhage.

In most textbooks little or no emphasis is placed on the irregularities that may be noted in the fetal heart tone. These alterations may be noted (a) during the latter part of pregnancy, before labor has begun, or (b) after labor has developed. In the first instance (before labor), marked irregularity may be noted occasionally; this is at times transient, at times rather persistent. Naturally, one thinks that the baby is in danger, and that there must be some interference with the fetal circulation. This may be so, and it is probable that, in case of intrauterine fetal death, cardiac irregularity may precede the death of the fetus; however, I have never observed this phenomenon. I have discovered marked irregularity of the fetal heart several times on routine prenatal examination, with subsequent delivery of an absolutely normal infant. One such instance was noted recently. The irregularity was so marked that the fetal pulse could not be counted. This condition was found on every examination over a period of several weeks; I considered the possibility of a cranial defect, but the x-ray showed a normal skull. After an uneventful labor, a healthy child was delivered, the heart was negative, and the postnatal pulse has been perfectly regular. I can offer no explanation for this state of affairs.

Of considerable importance, of course, is irregularity of the fetal heart during labor. It is essential, however, to consider the time of this irregularity in relation to the uterine contractions. It will be noted frequently during the labor pains, and for a few seconds after the cessation of each pain. The heart rate will then become perfectly regular and of the normal rate. This variation in the rate has no significance. At times, however, there will be an irregularity for about one-third or even one-half the interval, between the pains, then normal rate and rhythm will be resumed. This generally means that the cord is around the neck, and that there is not very much slack, so that there is some tension on this coil during the contraction. If there is plenty of slack, this slowing will not be noted. There is no danger to the child in such circumstances. One can at such times astonish the attendants by predicting that the cord will be found around the neck. On the other hand, if the irregularity persists for the entire period between the uterine contractions, the baby is generally in serious danger and delivery should be expedited if it is possible to do so. If pituitary extract has been administered, and the pains have become unduly strong and the interval is markedly shortened, irregularity of the fetal heart will be noted and signifies fetal distress. Fortunately, the effect of the pituitary extract is usually transient and normal conditions are soon re-established. If not, immediate delivery, if feasible, is indicated; if this is not possible, deep anesthesia to relax the uterus is necessary.

Now, as regards the presence of meconium in the amniotic fluid in vertex presentations, I feel that undue emphasis has been placed upon this occurrence, and that it is not always an indication of fetal distress, as obstetric literature would lead us to believe. This is particularly true if quinine has been given for the purpose of aiding in the induction of labor. But in patients receiving no quinine, we will frequently observe, when the membranes rupture, that the amniotic fluid is stained to a variable extent with meconium. If the heart tones are regular and of the normal rate, and if the pains are not too intense or too frequent, one can wait and let labor progress until delivery can be safely expedited. I do not feel that this development should be ignored entirely, but I am of the opinion that it should not be allowed to hurry us to the extent that difficult forceps extraction or version would be performed. Provided the baby appears to be in good condition, and the labor is progressing satisfactorily, a reasonable period of watchful waiting will usually be found to be the best procedure. Individualization is of prime importance under these circumstances.

its maximum at the free end of the leaflet, where the outline was irregular and the leaflet was markedly thickened. The vascular spaces could be identified in the leaflet, as is normal in this age group. A bit of mediastinal fat displayed a rather extensive area in which the red cells had been extravasated and the tissues were necrotic, and there was a scattered infiltration of polymorphonuclear leucocytes and occasional lymphocytes.

*Liver:* The normal architecture of the liver was markedly distorted. The liver cells were enlarged and often confluent areas were present as mere necrotic shells or replaced by pink-stained granular debris and nuclear debris. The sinuses in these areas were distended with red cells or the remains of blood cells, and the cellular structure was lost. Irregularly arranged about the margins of these areas, more or less well-preserved liver cells, grading through cells in various stages of degeneration into necrotic areas, were seen. In instances these parenchymal cells were of moderate size, with finely granular cytoplasm. In many instances there was more or less marked fine to coarse vacuolation or coarse granulation of the cytoplasm. The nuclei varied in their staining qualities, and a rather considerable amount of coarse brown granular pigment was deposited in the cells. The distortion of the necrosis was irregular, but in the main it appeared to be more pronounced about the portal spaces, while the better preserved liver cells tended to be distended about the central veins, giving the necrosis roughly a marginal or periportal distortion. The section was almost entirely devoid of leucocytic infiltration.

*Kidney:* Immediately under the cortex an occasional extravasation of blood was seen. Elsewhere the glomeruli were rather small, the cells were compactly arranged and deeply stained, as is characteristic of this age group. Bowman's space was free of contents. The tubular epithelium displayed a coarsely granular cytoplasm, their cell outlines were swollen, and the free borders of the cells were often ragged. The nuclei were variable in their staining qualities, many were pale, and in numerous instances the nuclei were missing. Granular debris was present rather abundantly in the tubular lumina. The blood vessels were moderately distended with red cells.

#### CONCLUSION

A case is reported in which the death of the newborn child was the result of a high fever of undetermined origin in the mother. It is of particular interest to note that the effect of this toxemia on the baby was to produce a type of liver destruction similar to that seen in the livers of patients dying of eclampsia.

2155 CLEVELAND AVENUE

### SOME OBSERVATIONS REGARDING THE FETAL HEART TONES AND THE PRESENCE OF MECONIUM DURING THE COURSE OF LABOR\*

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(From the Department of Obstetrics, Tulane University, School of Medicine)

THE auscultation of the fetal heart during labor is a matter of routine in every well-conducted obstetric case, and the importance of this simple act cannot be overestimated. However, there are a few points which might be mentioned in this connection which I feel may be of interest, especially since I find no mention of these details in obstetric textbooks.

In the first place, I wish to protest against the widely published admonitions to the effect that fetal danger is indicated by a pulse rate over 160 or under 100. In my experience, the upper figure is too low; in many instances I have noted rates of 170 or 180 during labor, with regular rhythms, followed by the deliveries of normal babies, whose resuscitation was not difficult. In one case, the fetal heart

\*Presented at a meeting of the New Orleans Gynecological and Obstetrical Society, June 1, 1939.

Baby girls infected with gonorrhea were treated by daily instillations of oil into the vagina.

The urethra and bladder in all gonorrheal cases were, of course, treated at the same time by standardized methods of irrigations, injections, dilatations, etc.

Practically every patient also received one of the several preparations of sulfanilamide either by mouth or hypodermatically.

Smears for gonococci became negative after two or three weeks' treatment in almost all cases, although a few remained positive for as long as eight weeks. There was also a definite decrease in the number of other bacteria that normally flourish in the vaginal and cervical secretions.

Profuse discharges stopped promptly, and cervical erosions were covered with healthy epithelium in a comparatively short period of time. In many cases there also seemed to be a definite lowering of the pH of the vaginal secretion with a return to normal acidity.

Patients all seemed to appreciate the immediate soothing effect of the oil as well as the absence of staining that results from the use of various dye preparations.

### CONCLUSIONS

The use of antiseptic oil appears to be a valuable adjunct in the treatment of infections of the cervix and vagina.

The above conclusion is based on the treatment of approximately 150 such cases.

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## A SAFETY LABOR BED

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(From the Emory Hospital)

INCREASING use of the amnesic method of relief of pain in labor by the use of drugs which obliterate the memory of events in labor, has necessitated more constant nursing supervision of the patient, to prevent infection from self-contamination of the vulva and injury from accidental rolling off the bed.

Mental excitation under this treatment varies with the temperament of the patient and the drugs used, but in some cases the patient may be very restless, trying to sit up and flinging her arms and legs about in forcible, incoordinate movements. During the pains she may subconsciously try to alleviate her discomfort by pressing her fingers against the vulva and thus infect herself unless restrained by the nurse.

Heretofore, accidental rolling off the bed, has been prevented by fastening boards or rails to the sides of the bed or using the crib type of bed with perpendicular metal sides which can be raised into position.

The objections to this type of bed are that the patient may become apprehensive prior to the induction of amnesia by the implied necessity of restraint and after she has been rendered amnesic, she may bruise her arms or legs by striking them against the metal sides. Furthermore, there is the added objection of the interference with the nursing and medical care of the patient, offered by the perpendicular metal sides.

To overcome these objections, the "trough" type of bed shown in Fig. 1 was devised by me.\* It has been used at the Emory Hospital with good results.

On admission to the labor room, the patient is put in what, to her, is an ordinary conventional-appearing bed. When she has reached the stage of labor indicated

\*Manufactured by the Comper Manufacturing Company of Pittsfield, Mass.

My reason for discussing the matter is that these details are not sufficiently clarified in obstetric literature and hence erroneous ideas are implanted, especially in the minds of medical students. I believe that it should be made clear that a rapid heart rate, even 170 or 180, if regular, is not necessarily a cause for great alarm, provided the pains are not unduly strong nor too close together. On the other hand, should one wait for the heart rate to drop to 100 before becoming uneasy, one will frequently deliver a dead or a seriously damaged baby. Furthermore, it should be made plain that the presence of meconium in the amniotic fluid in vertex presentations deserves serious consideration, but that it does not always mean grave danger to the baby, and hence should not of itself cause us to resort to a difficult operative delivery.

## THE USE OF ANTISEPTIC OIL IN THE TREATMENT OF VAGINAL AND CERVICAL INFECTIONS\*

W. A. REED, M.D., NEW ORLEANS, LA.

THE continual and persistent use of oily preparations from the earliest recorded time is indisputable evidence of their value in the treatment of infections. Microscopic studies of various tissues treated with oils show that the thinner vegetable oils are capable of quite considerable penetration into the deeper layers of the skin.<sup>1</sup> This penetration is undoubtedly aided by capillary action when the oil is applied to surfaces rich in glandular structures, such as the cervix uteri.

Judkin<sup>2</sup> in 1917 reported 25 cases of wound infections treated by local applications of liquid petrolatum, with rapid healing and excellent results. He believed that its virtue lay in the fact that the "low specific gravity of the oil allowed it to penetrate into all infected pockets," and that it "further promoted healing by encapsulation of the bacteria."

Recently the use of one of the commercial antiseptic oils has been adopted as the procedure of choice in the care of the skin of newborn infants. It was found to be particularly efficacious in the prevention of bullous impetigo of the newborn, pemphigus neonatorum, and dermatitis exfoliativa neonatorum, the etiology of which is the staphylococcus aureus.

The study reported here deals with the treatment of approximately 150 cases of cervical and vaginal infections of various types. About half of them were gonorrheal in origin, while the remainder were due to *Trichomonas vaginalis*, senile vaginitis, infections resulting from cervical lacerations, simple nonspecific endocervicitis, etc.

After many years of experience with various medications and suppositories, it was decided to experiment with one of the better known commercial antiseptic oils.

The plan of treatment was to first thoroughly irrigate the vagina with some warm antiseptic solution, such as permanganate of potash, and then apply a tampon soaked in the oil directly against the cervix, to be removed by the patient from four to twelve hours later. Antiseptic douches of choice were also used at home once or twice daily. The oil tampons were applied every second day for the first week, then twice a week for the following two or three weeks, and then once each week thereafter.

In cases of *Trichomonas vaginalis*, smears failed to show the organisms after two or three treatments, although in a small number of patients smears again became positive a few months after all treatment was stopped. Whether these were true recurrences or new infections could not be determined.

\*The preparation employed is that marketed by the Mennen Company. It includes hydroquinone, hydroxy-quinoline and chlorbutanol, dissolved in sesame oil as a vehicle.

# A MEMBRANOUS CAST OF THE UTERUS, TUBES, AND CERVIX

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*(From the Department of Obstetrics and Gynecology, Emory University School of Medicine)*

MEMBRANOUS dysmenorrhea is fortunately not very common, but complete casts of the endometrium are by no means rare. I can find no record, however, of an intact cast of the entire upper tubular tract having been extruded.

A white, married nullipara, aged 27 years, had dysmenorrhea since the onset of menstruation at the age of 13. Periods occurred every twenty-eight days and lasted seven to eight days. Membranous casts were first noticed at the age of 20 and on several occasions intact casts of endometrium were passed.



Fig. 1.—The constriction of the upper fourth of the endometrial portion of the specimen was produced by string used in mounting.

The family history was irrelevant and the personal history disclosed nothing more important than occasional urticaria and angioneurotic edema. General and pelvic examinations disclosed no abnormality.

A specimen passed January 4, 1939, was remarkable in that it consisted of a perfect cast of the mucosa of the Fallopian tubes, uterus, and cervix in one piece (Fig. 1). Microscopic sections of the cast were not made because the patient had preserved it in boric acid solution instead of alcohol. Aspiration biopsy twenty-four hours before onset of a menstrual period revealed normal premenstrual endometrium.

Treatment, including antiallergic regimen, calcium, and many hormone preparations, has been unsuccessful. A dilatation and curettement performed at the time of an emergency appendectomy did not even improve the subsequent period. There has been no change in the menses since marriage eighteen months ago.

for induction of amnesia, the head may be raised by the Gatch mechanism (*A*) to facilitate oral administration and retention of the drug. When amnesia has been effected and the patient begins to sleep, the head elevation is lowered and a section, ten inches in width, along the entire length of each side of the bed (*B*) is raised (simultaneously) to an angle of 45 degrees, by downward pressure on the foot pedal (*C*) which can be notched securely in this position.

This creates a trough which effectively prevents the patient's rolling off the bed. Since the mattress slightly overlaps the elevated sides, the patient cannot injure herself, regardless of how violent she may be. The rings (*D*) permit reasonable restraint of the patient's arms near the sides of the bed, by means of padded leather cuffs which not only prevents self-contamination of the vulva, but prevents any coordination of effort to get out of bed. It is impossible for the patient to raise

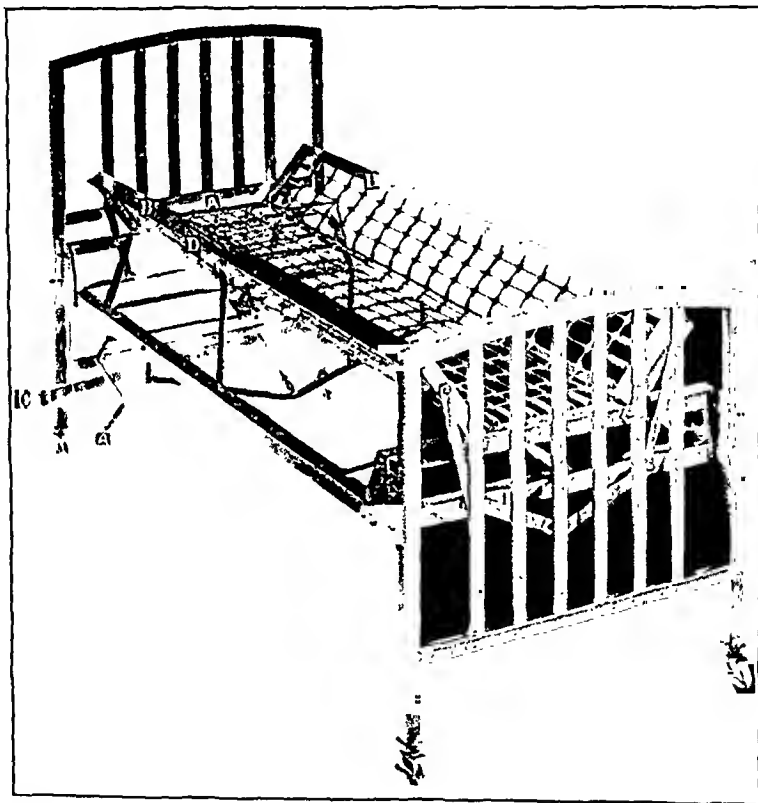


Fig. 1.—Showing bed with sides raised. The latter are flattened out when patient is placed on bed.

her hips over the raised sides. There is no interference with rectal or abdominal examinations or nursing care of the patient. The bed is large enough for obese patients, and, being of standard width, it can be readily moved from one room to another. The nurse is relieved of much physical strain in controlling the patient, and the hospital and the physician are assured that the patient cannot injure herself.

The safety labor bed, while devised primarily for obstetric use in amnesic or eclamptic cases, is of definite value in medical or surgical cases, as in comatose, irrational or postanesthesia cases.



I believe, limit their value." Concluding, he states, "Careful pelvimetry, the use of the impression method . . . and the study of serial roentgenograms of the bony pelvis and the fetal head in those cases in which the head fails to engage as term is approached, will enable one to more nearly approach that obstetric ideal which is the aim and desire of all." Harris states cogently that in the State of Michigan 21 per cent of patients have been delivered without benefit of *any* type of pelvimetry.

Speaking of a swing toward a stereomobile concept as against the museum concept of the pelvis, I wish to signalize the contribution of Caldwell of Columbia University. In agreement with Harris, he avers, "By the use of stereoroentgenograms disproportion between the head and the pelvis can be seen and a borderline case recognized as such. But in most instances the proper degree of significance which should be attached to this known degree of disproportion cannot be determined usually until after a trial of labor."

Caldwell, the originator of a new school of dystocic psychology, examines patients by x-ray before, during, after, and in between. He has charted the pelvis usefully, but his charts are replete with figures and characters which are for the present, at least, puzzling to the average clinician who must still navigate by crude reckoning. Caldwell has perfected his equipment, mental and physical, to a point where he seems almost to stand within a pelvis of familiar contours and directs the course of the fetal head by (to him) familiar laws of physics. If Caldwell's contribution to this meeting is perhaps a bit abstruse, it is, on the other hand, a most important one, and not alone to this program, but also to the welfare of the mothers and babies of the future.

Titus' treatise on indications for forceps application and delivery is an epitome. He gives a kindergarten consideration of types of forceps, their functions and contraindications. His presentation of the indications for forceps delivery, quoted from his recent text, may be considered classic. He seems to have found an almost ideal psychologic approach to this much abused obstetric operation.

Titus approves of so-called "prophylactic forceps operations." He says, "A trained obstetrician may be warranted under ideal hospital working conditions in shortening the time limit for low forceps, previously mentioned as one hour with the head on the perineum without advance." Opposing Plass and others, he advocates this procedure with the free use of episiotomy as truly a conservative measure, qualifying his championship by the following statement: "Forceps delivery of any type can be made a serious operation in the hands of men whose obstetric work is merely a small part of their entire practice, or where conditions are unsuitable for asepsis and good surgical technique."

Titus does not discard high forceps, but infers that the operation may occasionally be justified (Harris and Danforth to the contrary notwithstanding). He demands that only a trained obstetric operator shall undertake such a procedure and advocates the use of Piper forceps on the aftercoming head. Proof that Danforth's paper is written with teaching intent appears in his argument favoring episiotomy. The mediolateral episiotomy is applauded. The dangers of midline episiotomy are correctly presented. He has never seen the need to use bilateral episiotomy. Relative to so-called ironing of the perineum, Danforth says cogently: "It is of little importance to the woman whether her levators are separated by the advancing head or by the hand of an overenergetic doctor—the result to her is quite the same."

Herbert Miller of Yale draws interesting deductions relative to the actual responsibility of cesarean section in fetal mortality rates. Miller is a pediatrician, perhaps more a logician and mathematician, in this particular setting. He presents "the fallacies in the arguments both for and against operative delivery." Miller proves to his certain satisfaction that the *premature* infant birth weight is tremendously important in infant mortality rates in general. Birth weight determines survival. Correcting and recorrecting mortality rates in view of these deductions, Miller finally exonerates cesarean section from actual responsibility in the high fetal mortality rate which accompanies it. Its corrected mortality rate is not more than that of other types of delivery with the exception of breech extraction and

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## GENERAL SUMMARY OF THE SESSIONS ON OBSTETRICS OF THE FIRST AMERICAN CONGRESS ON OBSTETRICS AND GYNECOLOGY\*

GOODRICH C. SCHAUFFLER, M.D., PORTLAND, ORE.

CHARACTERIZING this effort to consolidate the obstetric data offered to the American Congress, it has been remarked that it is indeed difficult to redistill a distillate. Papers presented before these sessions are in the main epitomes. Were it not for the impressive experience and weight of authority which lies behind much that has been presented, a good deal of the material offered to the Congress might be said to be composed of commonplaces. Nearly all of the speakers on this program have quoted at considerable length. Your reviewer submits with absolute candor that in most instances the authors' own statements bear more of the weight of vested authority than those which he has quoted. The effort to select material for this report will of necessity have been dictated chiefly by the reviewer's personal interest more than by any well-advised critique. The result is, of necessity, haphazard—but the intention is definitely to be helpful—especially to those who have heard only a part, or perhaps none, of the proceedings of the Congress.

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### THE SECOND STAGE OF LABOR

Considerations of the second stage, including dystocia, forceps, breech, and general complications, have been discussed by Harris, Caldwell, Titus, Danforth, Cosgrove, and Rucker. Attention may be called to a statement made by Harris of the University of Wisconsin. He says, "External pelvimetry of the superior strait has its chief value in *classification* of contracted pelves rather than in their *recognition*." This statement should be emphasized as illustrating the trend away from academic architectural considerations of the pelvis toward a functional stereomobile concept of the pelvis in labor. The museum type of pelvic classification is giving way to the working concepts of Caldwell and Moloy, Thoms and others. Qualifying this statement, Harris continues, "In spite of valuable additions to our knowledge of the subject in the past few years, the accurate diagnosis of pelvic contractions has not been freed of its technical difficulty. Of the two methods of pelvic mensuration in common use manual pelvimetry is the oldest, most widely used and perhaps the most valuable." He is on the side of the majority of clinicians when he states "many have experienced technical and interpretative difficulties with the roentgenographic methods of pelvimetry, which for the present,

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\*This paper was presented in extended form before the General Sessions of the American Congress on Obstetrics and Gynecology at Cleveland, Ohio, September 11 to 15, 1939. From this report gynecologic subjects have been omitted as have papers to be published in this JOURNAL and one or two manuscripts not made available to the reviewer.

dilatation or version, in preference to sustaining the individual against blood loss, and instituting prompt and proper operative intervention—first supportive measures, then cesarean."

Calkins suggests rather timorously that even granted a positive diagnosis, it may occasionally, under ideal circumstances, be advantageous to wait in the interests of a more mature baby. By both authors this question is left as it has been in the past, an open one.

The too frequently neglected danger of tragic hemorrhage resulting from vaginal examination is mentioned. Rectal examination should be included in the same warning. Preparations for immediate operative intervention should be completed prior to such examination. Beyond this it is trite but true that the failure to administer blood where it is available, from whatever satisfactory source, leaves the physician open to just criticism.

Litzenberg, Studdiford, Schumann, and Cooke discuss post-partum hemorrhage and the management of the third stage. Litzenberg of the University of Minnesota says that post-partum bleeding following delivery in excess of 500 c.c., is commonly regarded as hemorrhage—that the average justifiable blood loss is 250 c.c. Unfortunately the average blood loss is, actually, he believes, 600 to 700 c.c. Studdiford, of Bellevue, quotes an incidence of pathologic bleeding of 10.5 per cent. Following spontaneous delivery pathologic bleeding occurred in one of each 8 patients. Following midforceps delivery, it occurred in one of each four patients. The incidence of abnormal bleeding, then, seems to parallel difficulty in delivery. The general mortality in post-partum hemorrhage groups is 3.8 per cent. Careful observation of statistics proves that attention to details in management of the third stage can definitely reduce the incidence of serious post-partum bleeding. Factors most often criticized are: efforts to express the placenta prior to its separation; failure to express the placenta once it is separated; failure to account for retained placental fragments; failure to discover and repair tears; failure to anticipate hemorrhage in the presence of uterine inertia or a history of former puerperal hemorrhage.

These speakers seem agreed that obstetric pituitary at the end of the first stage is helpful, although Allen, of Chicago, cordially disagrees. They also approve of the use of a reliable ergot preparation intramuscularly following delivery of the placenta. Studdiford noted incarceration of the placenta and increased difficulty in its delivery when ergot was used at the end of the second stage, although Schumann does not regard this possibility seriously. None of these authors puts sufficient emphasis upon the indications for uterine packing, nor is the procedure described. Failure to be prepared to pack and neglect to do so immediately is more frequently and more primarily a cause of death than failure to transfuse.

Manual removal of the placenta is not necessarily to be feared and under the proper auspices and indications, may perhaps wisely be used earlier and more often than it is. In general however, conservatism is advised. Schumann and Cooke underscore the necessity for preparation for hysterectomy, transfusion, or both on the least suspicion of placenta accreta. Schumann knows of four women in whom a placenta accreta was left strictly alone, after packing. All recovered.

Studdiford has discontinued the use of gum acacia solutions because of resultant catastrophes. He voices his suspicion that stored blood does not offer advantages comparable to direct transfusion. The importance of late unexpected post-partum hemorrhage is mentioned and should be stressed. Sudden, unexpected, and severe bleeding after the patient has been returned to her bed should be anticipated and controlled more frequently than it is.

Cooke, of Galveston, discusses unusual hemorrhage in pregnancy. Of hydatidiform mole he says, "In the vast majority of cases the mole may be removed per vaginam without hysterectomy, provided an Aschheim-Zondek or Friedmann test is done every two weeks for about three months, once a month thereafter for a year, and immediately upon the appearance of any abnormal bleeding." The tremendous importance of the application of these special tests to this condition should be signaled. Discussing rupture of the uterus thoughtfully, Krupp avers, "The great majority of cases of rupture at the present time occur as the result of the giving of pituitrin before the cervix is fully dilated or when there is obstruction

version and extraction. This, however, is not to be interpreted as inferring that cesarean section should replace breech delivery and version and extraction. He leaves us with one conclusion in which his logic is irrefutable: Breech delivery and version and extraction are inimical to low fetal mortality rates.

Rucker of the University of Virginia, in discussing breech presentation, states in a comparison of extended statistics that the gross fetal mortality averages 24 per cent. His own corrected mortality is 7 per cent. The average corrected mortality is 8 per cent. Premature deliveries give a higher percentage of breech presentations. The larger number of prematures among breech deliveries, therefore, increases the death rate.

Rucker agrees with Harris that external version to avoid breech delivery is wise. Bartholomew reduced the incidence of breech deliveries in his clinic to one-half its usual frequency by using external version, which is neither difficult nor dangerous, and safer without anesthesia.

In the conduct of breech delivery, the vital importance of supervision by an experienced, capable and level-headed attendant is paramount. Rucker says cogently, "The first requisite for the successful conduct of breech delivery is a thorough knowledge of the lesions found at autopsy in the babies which do not survive such operations and that haste is to be avoided."

Rucker reserves cesarean section in breech to cases of definite cephalopelvic disproportion, with the occasional exception of an elderly primipara more than ordinarily committed to the concept of a live baby. He prefers the nonoperative and so far as possible, spontaneous breech delivery, facilitated by early and wide episiotomy.

#### ANALGESIA AND ANESTHESIA

Bartholomew of Atlanta counts mothers fortunate to have at their disposal the many anesthetic agents now available. Pride, of Memphis, found an almost ideal combination of "analgesic, amnesic and anesthetic, in amytal-morphine-scopolamine mixtures." He has had no ill effects on babies in 300 such cases. Bartholomew, is less euphoric; he states that the ideal method is yet to be found. "If by that is meant a method which will cause no restlessness, no excitement, no tendency to uterine inertia, no fetal apnea at birth, and a method invariably successful in producing complete amnesia—it is doubtful whether such a method will ever be found."

Bartholomew arrays the comparative advantages and disadvantages of all available agents. Perhaps because he has recently been using it, he appears to prefer paraldehyde. Bartholomew and Kane are pretty much in agreement. They believe that paraldehyde is one of the safest, if not *the* safest, and they intend to continue its use in spite of its minor disadvantages; namely that low forceps delivery must be routine, with added inhalation anesthesia; restraints are necessary; the taste and smell are obnoxious; rectal irritation, nausea and vomiting are frequent. The babies may be expected to breathe on the average of thirty seconds later than without paraldehyde.

Nembutal, ethylene, and cyclopropane merit further consideration. There is as yet no apparent trend away from morphine. The advocacy of morphine-scopolamine mixtures is not tinctured by sufficient critique. Spinal anesthesia (except for low cervical section) is appropriately ignored. Regional block is not stressed.

#### PREGNANCY HEMORRHAGE

Calkins of the University of Kansas and Vaux of Philadelphia discuss hemorrhage due to placenta previa. Calkins describes his own experiences. Vaux speaks objectively with the obvious purpose of teaching. The general maternal mortality of placenta previa is given as 10 per cent, the fetal mortality 40 to 50 per cent. Maternal mortality in both conditions is increased in relation to nearness to term and parity. A general tendency to observe the mother's interest primarily, accounts for a high fetal mortality. Observations relative to management cling to tradition: Calkins, candidly appraising his results, believes by hindsight that several babies might have been saved without additional danger to the mother, by cesarean section. Vaux says: "I have given up all attempts at manipulation manually, bag

complete cooperation between obstetrician and internist. Of rheumatic heart disease, even in pregnancy, he states: "We no longer consider it steadily and inexorably progressive." He discusses sanely the implications of heart disease in relation to marriage, child bearing, and abortion. He stresses the trend away from abortion under almost any circumstances. He observes that, "The first step in the prenatal care of a woman with cardiac findings is exact diagnosis. . . . By close supervision and energetic treatment of the slightest evidence of failure, most cardiac patients can be carried successfully through term." Jensen also believes that, "A survey of conditions throughout the country indicates that the use of cesarean section for heart disease is finding a sound clinical level." Of hypertensive cardiorenal disease, including eclamptic toxemias, he says, "There is considerable evidence that hypertension during pregnancy is not a fortuitous circumstance but a sign that the patient's cardiovascular renal system is constitutionally inferior and her childbearing life should be governed accordingly."

*The surgical, abdominal complications of pregnancy* are discussed by Phaneuf of Boston. Fibroids are to be dealt with according to the mechanical necessity but, in general, "pregnancy in a myomatous uterus in the majority of instances evolves without complications and delivery is effected by the ordinary means." A similar generalization will apply to ovarian neoplasms. Retroversion of the uterus may require special management—seldom, if ever, operative. *Appendicitis* in pregnancy constitutes an exceedingly serious problem because of failure of localization on account of the large uterus. During his training the author recalls having seen five women with appendicitis during pregnancy, all of whom died of general peritonitis. The extreme importance of early diagnosis and operation prior to rupture is stressed. Diseases of the biliary tract should, as a rule, yield sufficiently to medical treatment to allow a successful obstetric outcome. Conservative surgical intervention is occasionally indicated. Again, gastric and duodenal ulcer should yield sufficiently to medical treatment. Surgery if absolutely essential should be conservative. For intestinal obstruction, from whatever cause, early surgery is indicated—again conservative. Infected diverticula, ileitis, tumors of the bowel must all be considered. Pregnancy should not deter from employing the known methods of arriving at a diagnosis, including x-rays of the gastrointestinal tract. Resultant termination of the pregnancy is to be managed, if possible, even more conservatively than usual. To avoid this accident, the copious use of narcotics will be advisable. Phaneuf fails to mention the potential value of heavy doses of progestin—the possible value of wheat germ oil.

*Pyelitis in Pregnancy.*—Traut of the New York Lying-in Hospital points out the reasons for the frequency of lower urinary infections and the serious dangers which they entail. Traut has learned to recognize the very early signs of pyelitis by studying routine pregnancy urine specimens. Ambulatory treatment of patients with suspicious urine, with small doses of sulfanilamide, has markedly reduced the incidence of clinical pyelitis on his service. Special prophylactic attention is given to patients with a history of previous urinary infections. Large doses of sulfanilamide under careful observation are used in serious involvements. Criteria for cure are exacting. Post-partum pyelitis has been almost completely eliminated in his experience by prophylactic doses of sulfanilamide in all suspected patients. Traut offers a convincing and intensely helpful thesis. His observations dovetail neatly with recently published Mayo Clinic studies (Staulker, Schulte) relative to bacteriostasis in postoperative urine retention.

Discussing *endocrine aspects*, Novak, of Baltimore, and George Gray Ward, of New York, adhere to gynecologic applications. In a more general consideration, Allen, of Chicago, agrees with the others that "the indiscriminate use of (these) powerful catalytic agents, often prescribed without even an adequate physical examination for everything from falling hair to normal senility, will not enhance the trust in our profession and will only add to the financial burden of our patients. . . . We are beginning to quote treatment in thousands of units, even in millions. One is reminded of the present financial activities of our government; and the multiplicity of hormones ascribed to the pituitary alone is reminiscent of the A.A.A., N.R.A., or the W.P.A." Allen outlines an extremely useful program for study of the patient. He has a flair for figures of speech. Speaking of endometrial

to descent of the fetus. Most traumatic ruptures occur from roughly performed forceps operations or versions, especially the latter."

### PELVIC INFECTIONS

Goodall, of Montreal, Norris, of the University of Pennsylvania, and B. P. Watson, of Columbia, discuss pelvic infection. Goodall elucidates clearly the various modes of extension, emphasizing the great importance of migration of bacteria via mucous membranes. He is didactic—empiric in spots. For example, he might have some difficulty supporting his statement that "many of these cases (post-partum pelvic infections) are the outcome of trichomoniasis in the puerperal state." Furthermore, others might wish to temper his statement that "the mode of extension can be determined in almost every case, and that when the mode of extension has been determined, the complications which may devolve from each case are predetermined and are fully anticipated." This statement, for many of us, could be made only with reservations. His paper is replete with meaty fragments, some of which cry for further verification. This fundamental treatise on pelvic extension of infection, by the way, is an excellent companion piece to Arthur Curtis' illuminating study of modes of extension of cancer.

Norris epitomizes textbook concepts relative to pelvic infections. His absolute adherence to conservatism versus surgery in the management of these conditions is satisfying. He preaches the gospel of masterly inaction, with the occasional exception of colpotomy or localized drainage. Norris condenses his material so skillfully that he virtually proves that truisms need not be boring.

B. P. Watson, of Columbia, reports helpfully his conclusions from researches on the transmission of puerperal infection. He concludes that in sulfanilamide we have a drug which is almost the specific against this sort of infection and which may prove to be of prophylactic value when general streptococcal infections are prevalent."

### COMPLICATIONS OF PREGNANCY

*The Thyroid in Pregnancy.*—Lawrence Randall of the Mayo Clinic points out tersely and clearly that "the increase in activity of the thyroid gland in pregnancy is not a condition of hyperthyroidism but represents the response of the thyroid gland to the increase in metabolic demands of fetal and maternal tissue." The gland, under normal circumstances, is called upon for hyperfunction. Additional iodine is frequently needed to avert colloid formation. Further, colloid goiter and adenoma in the fetus will be averted by adequate iodine administration to the mother. Attention is called to a group of patients with lowered basal rates without myxedema, particularly in pregnancy. The details of thyroid administration are given, basal rate determinations governing the therapy. The danger of activation of an adenoma spontaneously or by the use of iodine in the pregnant woman is pointed out. The management of active adenoma and Graves' disease in pregnancy is discussed, considerations in general being similar to those outside of pregnancy.

Speaking of *tuberculosis and pregnancy*, Jameson, of Saranac, states the case briefly: "The occurrence of pregnancy in a woman with pulmonary tuberculosis is to be avoided if at all possible as it complicates the picture medically, economically and socially. . . . There is ample evidence at the present time, however, to lead us to believe that if the tuberculous woman receives adequate treatment for her pulmonary disease the pregnancy need not give rise to particular worry from a medical standpoint." Jameson points out cogently that whereas much has been done to care for certain classes of tuberculous patients, the pregnant tuberculous woman is woefully neglected. The management of tuberculosis in pregnancy is, ideally, the proper management of both conditions. Abortion for pulmonary tuberculosis is seldom, if ever, justifiable. If it is employed it should never be after the twelfth week. Collapse therapy during pregnancy may be wise. Cesarean section may have an advantageous place in the delivery of the tuberculous woman.

Relative to *heart disease and pregnancy*, Jensen, of Washington University, states that "Among the profession as a whole the diagnosis and treatment of heart disease in pregnant women is still very inadequate." He underlines the necessity for

# Department of Reviews and Abstracts

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CONDUCTED BY HUGO EHRENFEST, M.D.

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## Selected Abstracts

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### Stilbestrol and Testosterone

Karnaky, K. J.: *Clinical Use of the New Synthetic Estrogenic Hormone, Stilbestrol*, South. M. J. 32: 813, 1939.

This is a preliminary report upon the use of a synthesized potent estrogenic hormone which is effective when administered orally. Structurally, diethylstilbestrol is quite unlike estrone, yet it possesses similar physiologic properties. One milligram is equivalent to 25,000 International Units of estrone when taken by mouth.

Animal experimentation has indicated that it has a low toxicity and a wide margin of safety therapeutically. In a few patients nausea followed its administration, but this was avoided by taking the medication after meals or at bedtime.

It was successfully employed in the treatment of a number of conditions. Excellent results were obtained in the postmenopausal syndrome with considerable subjective and objective improvement; the thin senile vaginal mucosa assumed the characteristics of healthy adult mucosa, and the hydrogen ion concentration changed from alkaline to normal acid reaction following a course of therapy. The claim is made that stilbestrol is 90 to 95 per cent effective in the treatment of functional bleeding. Endometrial biopsies revealed anatomic improvement within forty-eight to seventy-two hours. The prescribed dose was 0.1 mg., two to three times daily, or the entire amount at bedtime. Gonorrheal vaginitis responded well. Oral administration of this hormone is particularly suitable and convenient in the treatment of gonorrheal vaginitis of children.

ARNOLD GOLDBERGER.

Bishop, P. M. F., Boycott, M., and Zuckerman, S.: *The Estrogenic Properties of Stilbestrol (Diethyl-Stilbestrol)*, Lancet 1: 5, 1939.

In recent years attention has been directed toward the estrogenic activity of synthetic compounds which may or may not in common with the naturally occurring estrogens contain the phenanthrene ring. A compound containing 2 benzene rings (diethylstilbestrol) was described by Dodds and his co-workers in 1938 and found to compare favorably biologically with the natural estrogens and to be active by mouth. It was administered to 18 patients with amenorrhea of variable duration and resulted in estrin withdrawal bleeding in 8 and rhythmic uterine bleeding in 2 additional patients; 6 patients did not respond though they had previously shown withdrawal bleeding following therapy with estradiol benzoate. One patient had shown no response with previous estrogenic therapy and the other failure had not received previous therapy. The total dosages used varied from 4 to 70 mg.

In a group of 25 patients with menopausal symptoms, response was obtained in 17. A dose of 0.1 mg. daily by mouth was sufficient in one case to produce relief of symptoms and a vaginal estrus smear in fourteen days although the improvement was not maintained.

biopsy, says he, "Our judgment based on these bits of tissue should be tempered by remembering that this handwriting by the ovaries on the wall of the uterus is not as legible or the same in all areas which the curet has explored."

In summary, the reviewer's effort has been to italicize first, recent obstetric developments and improvements now consolidated but not universally employed; second, for re-emphasis, the common abuses of good obstetric practice; third, for reiteration, basic obstetric epigrams. This threefold purpose will have been by no means completely fulfilled. The effort, however, has been to epitomize the important transactions of this Congress for that vast majority of obstetricians who have been unable to attend the sessions of the Congress. For the program itself, certain criticism may perhaps be justly leveled. When, however, the bitter critics of our profession can offer a program so openly devoted to self-critique, so consolidated in the interest of unselfish progress, we may feel more impressed by the bases of their judgment. Another Congress may perhaps achieve improvement in certain respects; but will not be grounded in any finer devotion to an excellent cause.

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Pearl, Raymond: *Fertility and Contraception in New York and Chicago*, J. A. M. A. 108: 1385, 1937.

New York and Chicago represent the farthest progression of the process of urbanization in the western hemisphere. This process has produced profound alterations both quantitative and qualitative in human reproduction. Certain aspects of the reproductive histories of 3,951 women dwelling in New York City and 3,589 dwelling in Chicago were analyzed and compared. All the women in both samples were living in wedlock, had been married only once, and were free of any recognized form of gynecologic disease.

The white women of the Chicago sample appear to be somewhat less fertile on the average than the white women of the New York sample, whether measured by pregnancies experienced or live births produced.

Attempted contraception was more frequent among the Chicago than among the New York white women, the percentage of contraceptors being 64 in the former city and 53 in the latter. Contraception as practiced was more effective among the New York women than among the Chicago women.

The data from both cities indicate that women practicing birth control resort to criminal abortion more frequently than do noncontraceptor women. There is reason to believe, and it is expected that later in another place it will be demonstrated, that New York and Chicago are in no wise peculiar in this respect but that the total material of over 30,000 reproductive histories will show the same thing. The abortionist is called on to rectify the inadequacies of birth control.

GROVER LIESE.



symptoms and in 10 women in whom it was desired to suppress lactation after labor. All of the menopausal patients were relieved of their symptoms. However, this new drug produces the same disagreeable disturbances as stilbestrol among these women. On the other hand, only one of the ten post-partum patients experienced intolerance of the drug. The author is at a loss to explain why post-partum patients are resistant to the toxic symptoms of this drug.

J. P. GREENHILL.

**Campbell, N. R., Dodds, E. C., Lawson, W., and Noble, R. L.: Biological Effects of the Synthetic Estrogen Hexestrol, *Lancet* 2: 312, 1939.**

A synthetic estrogenic substance called hexestrol (4:4'-dihydroxy- $\gamma$ :8-diphenyl-n-hexane) is evaluated in this report from the standpoint of its biologic effects in comparison with stilbestrol and natural estrogens.

It is found to sensitize the uterus of the ovariectomized rabbit to the action of progesterone and to stimulate the nipples and mammary glands. Impregnation in the rat was prevented by oral administration of hexestrol. Reduction of body growth and atrophy of the gonads followed its prolonged use in rats.

Hexestrol and stilbestrol produced approximately equal increases in the weight of the uterus of the immature rat. When assayed by injection into ovariectomized rats, hexestrol was found more active than stilbestrol, and both were two to three times more active than estrone. These two substances showed approximately the same degree of activity when given by mouth and when applied intravaginally.

CARL P. HUBER.

**Boling, J. L., and Hamilton, J. B.: The Effect of Synthetic Male Hormone Substance Upon Follicular Growth and Ovulation in the Guinea Pig, *Anat. Rec.* 73: 1, 1939.**

Adequate administration of synthetic male hormone substance, testosterone propionate, suppressed follicular growth and ovulation in 19 guinea pigs during a six- to eighteen-day period of injection. Ovulation was prevented as shown by (1) the lack of behavioral responses characteristic of guinea pig periods of heat and ovulation; (2) the failure of the vagina to open; (3) the atrophic condition of the ovaries as seen upon operative inspection, and (4) microscopic examination of the ovaries which showed (a) average volume and range of the largest active follicle about that of untreated guinea pigs on the fifth to eighth day of a sixteen-day cycle, (b) a large number of atretic follicles, and (c) no new corpora lutea. In 12 other females the continued administration of testosterone propionate prevented ovulation during nine months of injection.

The reproductive cycle and ovulation returned soon after the cessation of androgen injections; the vagina opened eight to thirteen days after the end of 6 to 18 injections in 10 of 11 animals observed thereafter. Some of these guinea pigs were found to be in a period of heat six to ten days after the opening of the vagina and two others were mated with subsequent bearing and rearing of normal offspring. Two more guinea pigs injected continuously for nine months bore and raised offspring when injections were stopped. Ovulation occurred in a shorter time after the cessation of injections than it does in a normal animal following a period of heat.

J. P. GREENHILL.

**Geist, Samuel H., Salmon, Udall J., and Gaines, Joseph A.: The Use of Testosterone Propionate in Functional Bleeding, *Endocrinology* 23: 784, 1938.**

Testosterone propionate (in doses of 300 to 1000 mg. per month) inhibits menstruation and arrests the endometrium at the early proliferative phase, preventing the development of progestational changes. Larger doses cause varying degrees of regression of the endometrium to the state of hypoplasia or atrophy. Following the discontinuation of therapy, the inhibitory effects on the endometrium

Two patients with dysmenorrhea obtained relief following daily 0.1 mg. tablets during the first half of the cycle.

Biopsy studies of the mammary epithelium were done in one patient who received 280 mg. of the synthetic hormone by mouth. Proliferation and increased activity of the epithelium was found but nothing suggesting any type of malignant change.

Nausea or vomiting was noted in three of 46 patients but did not depend upon the dosage.

Typical proliferation of the endometrium was demonstrated both in the human being and in the monkey. In the spayed rhesus monkey, a single injection of 0.5 mg. of stilbestrol in oil is sufficient to produce vaginal bleeding after an interval of about twelve days.

CARL P. HUBER.

Palmer, A., and Zuckerman, S.: Further Observations on the Similarity of Stilboestrol and Natural Oestrogenic Agents, *Lancet* 1: 933, 1939.

Diethyl-stilbestrol has been shown to have the following properties in common with the natural estrogens: (1) It produces estrus in ovariectomized rats and mice by injection; (2) it causes growth of the endometrium in rats, rabbits, and monkeys and activates the sexual skin in the latter; (3) it causes changes in the feathers of capons and in the teats of guinea pigs; (4) it substitutes for the natural estrogens in the treatment of women with symptoms resulting from hypofunction of the ovaries; (5) it interrupts early pregnancy in the rabbit; (6) it inhibits the gonadotropic activity of the anterior pituitary in rats. It differs from the natural estrogens in that it is much more active by mouth.

The authors have shown that stilbestrol will sensitize the endometrium of the spayed monkey to allow for progestational differentiation. They have shown that it is active equally with estrone when applied intravaginally in oil to spayed mice. They were able to produce estrus in spayed mice also by the percutaneous absorption of stilbestrol in oil painted on the neck.

CARL P. HUBER.

Moricard, R., and Saulnier, F.: Comparative Study on the Activity of Diethyl-stilboesterol and Oestradiol Benzoate in Human Therapy, *Ann. d'endocrinol.* 1: 215, 1939.

The authors treated 12 patients, 11 of whom had been previously treated with estradiol benzoate or gonadotrophic hormone, with diethyl-stilbestrol, 1.0 mg. per day for ten days, and compared the results.

Eight of the 12 cases were surgical castrates. The authors' cases show that 7 of the 11 patients treated with estradiol or gonadotrophic hormone obtained symptomatic relief, 2 experienced partial relief, while 2 others secured no relief. Diethyl-stilbestrol gave symptomatic relief to 4, partial relief to 3, and no relief to 5 cases. In 2 of the last 5 cases the symptoms were actually made worse. Seven of the 12 patients experienced moderate to severe gastrointestinal disturbances, in fact, it became necessary to discontinue treatment in 3 of the cases because of these upsets.

Two of the surgical castrates had vulvar ovarian grafts which responded moderately to gonadotrophic hormone but in both cases these grafts responded much more rapidly and intensely to the diethyl-stilbestrol treatment.

The authors conclude that estradiol benzoate, in view of its nontoxicity, remains the basis of gynecologic hormonal therapy.

CLAIR E. FOLSONE.

Varangot, J.: Estrogen Activity and Toxicity of Dihydroxy-diphenyl-hexane, *Bull. Soc. d'obst. et de gynéc.* 28: 426, 1939.

The author reports his results with a new synthetic preparation of estrin very similar to stilbestrol. The drug was used in 25 women who had menopausal

occurred in women who were nervous after the hypodermics and refused to continue with the treatment. In the 38 successful cases the menses became regular in frequency and amount and the uteri diminished in size. The author is enthusiastic about this form of therapy and believes it should be helpful in cases of vaginal bleeding also. He had one such successful case. He believes that testosterone may be used to overcome the disagreeable symptoms which some women have just before the menses.

J. P. GREENHILL.

Mazer, Milton, and Mazer, Charles: *The Effect of Prolonged Testosterone Propionate Administration on the Immature and Adult Female Rat*, *Endocrinology* 24: 175, 1939.

In the immature rat, prolonged administration of testosterone propionate causes a decrease in the weight of the pituitary, adrenals, ovaries, and uterine horns and inhibition of estrus with mucification of the vaginal epithelium. The degree of uterine atrophy is not in proportion to the ovarian atrophy, presumably because the suppression of estrogen production is partly counterbalanced by the direct stimulative effect of testosterone on the uterus. The adult rat reacts similarly with the exception that the pituitary gland shows no significant decrease in weight. The deleterious effect of prolonged testosterone treatment on the ovaries is temporary. Restitution of structure and function occurs within twenty-nine days.

Evidence is drawn from the literature and the experiments described that the duration of treatment is the determining factor in the effect of testosterone on the ovaries; short treatment produces stimulation and prolonged treatment depression. It is considered that the ovarian atrophy here described is secondary to pituitary inhibition.

J. THORNWELL WITHERSPOON.

Desmaret and Mme. Căpitan: *The Value of Testosterone Treatment in the Menometrorrhagias and Menopausal Disorders*, *Presse méd.* No. 51, p. 1031, 1939.

In a previous study of testosterone treatment in mastopathy cases, the authors observed that some of these patients, who had an associated hypermenorrhea or menorrhagia, obtained a favorable return to normal menstrual periods. This observation inspired the present study.

After ruling out local and systemic causes of menorrhagia, the authors were able to group the uterine hemorrhage cases into two groups: (1) young women giving a previous history of difficult labors, puerperal hemorrhage, or an earlier abortion which had not been treated by curettage, and (2) menorrhagias appearing in the premenopausal period. The bulk of patients were in the latter group.

In general the treatment used was a series of hypodermic injections of testosterone propionate, each 10 mg., beginning the ninth day after the onset of the menses and every second day thereafter until a usual total dosage of 80 mg. was reached. In the following months it was usually necessary to decrease the dosage considerably, or to even discontinue the drug. The dosage of testosterone given to each patient must be judged by the individual patient's response.

Due to an imbalance of ovarian and hypophyseal secretions, the patients evidence endocrine dysfunction characterized by symptomatic periods of menorrhagia or amenorrhea. The authors feel that these fluctuating secretory levels not only affect other endocrine glands but the whole organism including the vegetative nervous system.

For those patients with vasomotor symptoms in the premenopausal period without hemorrhages, the writers recommend a combination of testosterone acetate (5 mg.), and one ampoule of gynestryl, three times a month, on every tenth day. Should the menses last longer than ten days, in periods preceding menopause, only a series of testosterone propionate, as previously outlined, is used.

gradually disappear and normal estrogen and progesterone effects reappear. It is suggested that the regressive changes noted in the endometrium after testosterone propionate administration are the end results of a primary inhibition of the gonadotropic factors of the hypophysis, causing suppression of the ovarian cycle, with consequent cessation of estrogen and progesterone production.

J. THORNWELL WITHERSPOON.

Phelps, Doris, Burch, John C., and Ellison, E. T.: Effect of Long-Term Injections of Testosterone Upon the Guinea-Pig Endometrium, *Endocrinology* 23: 458, 1938.

Adult female castrated guinea pigs were injected with 1 mg. of testosterone propionate daily for 26 (2 animals) or 34 (6 animals) days. Endometrial specimens from these animals were compared with similar specimens from adult guinea pigs which had received 2 R.U. of theelin daily for 21 (17 animals) or 30 to 40 (8 animals) days. Endometria from guinea pigs injected with testosterone showed typical Swiss-cheese dilatation of the glands, moderate proliferation of the surface epithelium, mild proliferation of the glandular epithelium and a mild reaction of the stroma. Endometria from guinea pigs injected with theelin showed typical Swiss-cheese dilatation of the glands, marked proliferation of the surface and glandular epithelium and a strong reaction of the stroma. The results indicate that: (a) the response of the guinea pig endometrium to testosterone is qualitatively similar to the response to theelin; (b) theelin and testosterone differ markedly in potency with respect to their effect upon the endometrium; and (c) cystic dilatation of the endometrial glands may result from the application of a stimulus which is, comparatively speaking, extremely weak.

J. T. WITHERSPOON.

Béclère, C.: Testosterone Propionate in the Treatment of Uterine Hemorrhages, *Bull. Soc. d'obst. et de gynéc.* 27: 747, 1938.

Béclère reports a series of 14 women who were treated with testosterone propionate for uterine hemorrhages and who were followed from four to six months. The results were highly favorable. Six women were in the premenopausal age between 45 and 55 years of age. They were given moderate doses, usually 25 mg. a month. The results were good in all the cases.

Among seven women who had functional bleeding due to genital infection, there were 5 favorable results and 2 failures. The last case was that of a woman who had bleeding associated with a submucous fibroid. The bleeding ceased following one injection of 25 mg. of testosterone propionate.

J. P. GREENHILL.

Palmer, R., and Moricard, R.: A Case of Submucous Myoma Treated by Testosterone Propionate, *Compt. rend. Soc. franç. de gynéc.* 8: 300, 1938.

Previously the authors reported that they could control uterine hemorrhage by the injection of estrin, progesterone, and urinary prolan. They also reported on the use of testosterone in 1936. They now describe a case in which they brought about a cessation of uterine bleeding by means of testosterone propionate but failed to influence the size of a submucous fibroid which was present. They verified the size of the fibroid by repeated hysterograms. The patient had bled profusely for eleven months, both at the time of the menses and during the intervals. She was given 5 mg. of testosterone every second day for three months, a total of 220 mg.

J. P. GREENHILL.

Bravarski, J.: The Use of Testosterone Propionate in Gynecology, *Bull. Soc. d'obst. et de gynéc.* 28: 418, 1939.

The author used testosterone propionate in 40 cases of metrorrhagia associated with fibroids of the uterus, and he met with success in 38 cases. The two failures

# Items

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## American Board of Obstetrics and Gynecology

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board at the Atlantic City Hospital, Atlantic City, N. J., from Friday, June 7, through Monday, June 10, 1940, prior to the opening of the annual meeting of the American Medical Association in New York City on Wednesday, June 12, 1940. Candidates are requested to note that the dates of the examinations have been advanced one day from those previously announced.

Application for admission to Group A, Part II, examinations must be on file in the Secretary's Office not later than March 15, 1940.

Formal notice of the time and place of these examinations will be sent each candidate several weeks in advance of the examination dates.

Candidates for *reexamination* in Part II must make written application to the Secretary's Office before April 15.

The annual dinner of the Board will be held in New York City on Wednesday evening, June 12, 1940, at the Hotel McAlpin.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

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## "The Foundation Prize" of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons

The award known as "The Foundation Prize" shall consist of \$150.00. Eligible contestants shall include only (a) interns, residents, or graduate students in Obstetrics, Gynecology or Abdominal Surgery, and (b) physicians (with an M.D. degree) who are actively practicing or teaching Obstetrics, Gynecology or Abdominal Surgery.

Manuscripts must be presented under a non-de-plume, which shall in no way indicate the author's identity, to the Secretary of the Association together with a sealed envelope bearing the non-de-plume and containing a card showing the name and address of the contestant.

Manuscripts must be limited to 5,000 words, and must be typewritten in double spacing on one side of the sheet. Ample margins should be provided. Illustrations should be limited to such as are required for a clear exposition of the thesis. Submit 3 copies of thesis and illustrations to secretary. The successful thesis shall become the property of the Association, but this provision shall in no way interfere with publication of the communication in the journal of the author's choice. Unsuccessful contributions will be returned promptly to their authors. All manuscripts entered in a given year must be in the hands of the Secretary before June 1.

The award will be made at the Annual Meetings of the Association, at which time the successful contestant must appear in person to present his contribution as a part of the regular scientific program, in conformity with the rules of the Association. The successful contestant must meet all expenses incident to this presentation.

The President of the Association shall annually appoint a Committee on Award, which, under its own regulations, shall determine the successful contestant and shall inform the Secretary of his name and address at least two weeks before the annual meeting.

JAS. R. BLOSS, M.D., Secretary.  
418 Eleventh Street, Huntington, W. Va.

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Attention is called to an important announcement on Advertising Pages 13 and 14.

The authors do not mention the number of patients treated with testosterone. They state, however, that the largest group was in the premenopausal period. Five cases are reported in detail. In Case 2 they add an interesting observation that the circumference of the patient's hips, thighs, and knees decreased in size and the patient lost 2 kg. of weight. The writers are enthusiastic about their good results but warn that every patient must have her treatment individualized.

CLAIR E. FOLSONE.

**Turpault: The Male Hormone in Women Especially in Cases of Hemorrhage, Gynécologie 38: 281, 1939.**

In the opinion of Turpault male hormones are indicated in women for the following conditions: mastopathies, uterine fibroids, functional uterine bleeding, especially at puberty and at the menopause, intermenstrual pain, uterine hyperplasia, hypertrophy of the cervix, and disturbances of the menopause. He cautions, however, that in addition to the favorable effects of the male hormone there are certain inconveniences. These are as follows: fatigue, which may be overcome by adrenal therapy, excitement, liver disturbances, deepening of the voice, and enlargement of the clitoris.

The dose of male hormone varies with the indications for its use. However, it is best to begin with small doses, such as 5 mg. For mastopathies, from 5 to 30 mg. should be given each month, distributed in from 1 to 5 doses, beginning the tenth day after the onset of the menses. For functional uterine bleeding, as much as 50 to 60 mg. must usually be given each month. For fibroids of the uterus very large doses, from 50 to 500 mg., must be administered.

Not infrequently after the hormone is stopped, the symptoms reappear. In such cases one may try implantation of testosterone in the form of crystals in the skin, as suggested by Parkes.

J. P. GREENHILL.

**Moricard, R., and Saulnier, F.: Artificial Development of the Genital Apparatus by Means of the Esters of Testosterone, Gynécologie 38: 272, 1939.**

These authors were able to produce a marked development of the genital apparatus in human beings by means of the synthetic esters of testosterone. This could be accomplished with 100 mg. administered over a period of a month and a half. When 400 mg. were given, there was an almost constant appearance of signs of puberty in children, who had the adiposogenital syndrome. Among women the injection of the esters of testosterone resulted in a disappearance of the neurovegetative symptoms of castration. Likewise this substance was capable of stopping functional uterine bleeding.

J. P. GREENHILL.

**Mascio, Aquino: The Action of Testosterone in Functional Uterine Haemorrhage, Folia demograph-gynaec. 36: 165, 1939.**

The author considers the mechanism of the therapeutic action of testosterone and reports results in several cases of functional uterine bleeding. With the doses employed by him (5 to 10 mg. on alternate days) no untoward effects were observed. He found a constant and favorable action in controlling functional uterine bleeding both in puberty and in the preclimacteric.

MARIO A. CASTALLO.

Pardee<sup>13</sup> and Reddick<sup>16</sup> agree, and express more or less the opinion of most cardiologists that the presence of heart disease per se is insufficient reason for terminating a pregnancy. The degree of involvement, the cardiac response to therapy, and other factors enter into the decision for or against therapeutic abortion. Schultz<sup>18</sup> emphasizes that interruption of the gestation should not be undertaken while the patient is decompensated.

The problem is less urgent in most of the vascular-renal disorders, says Herrick.<sup>8</sup> He admits, however, that smaller groups of patients with primary nephritis are more likely to need termination before the period of viability when the nephritic symptoms do not yield to treatment.

Ingraham<sup>10</sup> concludes in his study of tuberculosis that the operation of therapeutic abortion is justified if the expectancy of death is in the neighborhood of 50 per cent when pregnancy is allowed to continue. On the other hand, Burrell<sup>3, 4</sup> advises interruption not only for active and progressive cases, but for some stationary cases as well.

Most neurologists and psychiatrists seem to believe that psychic and neurologic disorders are not absolute indications for interruption. They subscribe to the doctrine that in certain individuals intervention is the procedure of choice. Singer<sup>19</sup> and Cheney<sup>5</sup> support this stand.

Heyneman<sup>7</sup> and Philipp<sup>14</sup> point out that when impairment of kidney function occurs in an unyielding pyelitis, the pregnancy should be sacrificed.

Throughout the literature it is emphasized that every case must be evaluated upon its own merits alone.

Taussig<sup>20</sup> describes various operations and procedures for therapeutic abortion. Mendenhall,<sup>11</sup> Portis,<sup>15</sup> Brindeau and Lantuéjoul,<sup>2</sup> Haultain,<sup>6</sup> and Holland<sup>9</sup> endorse combined abdominal hysterotomy and sterilization. The use of intra-uterine injections of formol as described by Boero<sup>1</sup> has not become popular. The use of x-ray therapy for destruction of the fetus was advocated by a few, never accepted by many, and now is in general disrepute.

Termination by dilatation and evacuation is the common practice in the first trimester of pregnancy, and properly so where ligation or resection of the tubes is not indicated. Moreover, it is almost universally agreed that therapeutic abortion should be distinctly less common after the fourth month of pregnancy.

In his discussion of therapeutic abortion, Morgan<sup>12</sup> calls attention to the need of adequate consultation, the importance of written consent from the husband and wife, and the merit of sterilization in properly selected cases.

## DISCUSSION

The physician who terminates a pregnancy before the fetus is viable assumes a heavy responsibility. He sacrifices one life on behalf of another. In the existing medicolegal aspects of the problem the physician clearly does not have the right, even though he may have the inclination, to act on social or economic grounds. The various states have different laws relative to the legal status of therapeutic abortion, but there are no recognized indications under any existing law except those pertaining to the life or health of the mother. According to Taussig,<sup>20</sup> in 6 states intentional abortion is forbidden with no legal exemptions; in 38 states saving the life of the mother is recognized as the only legal exception; in 3 states and the District of Columbia preservation of health is also recognized. Therefore, whatever the indication, a therapeutic abortion should not be undertaken except for medical reasons, and only after a consultation of at least two physicians, both of whom concur in the opinion that the procedure is necessary to preserve the life or health of the mother or, rarely, to prevent

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## LIMITATION OF HUMAN REPRODUCTION\*

### THERAPEUTIC ABORTION

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THERAPEUTIC abortion means the termination of an apparently normal intrauterine pregnancy before the period of viability in an effort to save or prolong the life of the mother. Between May 25, 1931, when the present institution was opened, and July 1, 1939, 134 pregnancies have been therapeutically terminated before the twenty-eighth week of gestation at the Chicago Lying-in Hospital and Dispensary. In the same period 26,131 mothers have been delivered at or near term, so that the ratio of therapeutic abortion to deliveries is 1 to 195. This figure is higher than a true cross section, for many cases were referred from outside agencies. A critical review of this material may help answer the important question, is therapeutic abortion always good therapy? Medical, and only medical, aspects are under discussion.

### REVIEW OF LITERATURE

Opinions rather than data make up the bulk of the literature on therapeutic abortion. Whitehouse<sup>21</sup> and Redenz<sup>17</sup> are exceptional in reporting large series of 690 and 500 cases, respectively. Cardiac disease, gestational toxemias, pulmonary tuberculosis, and neuropsychiatric disorders constituted the major groups in which both of these workers reported therapeutic termination of pregnancies before viability.

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NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."



TABLE I. CONDITIONS FOR WHICH THERAPEUTIC ABORTION WAS DONE

INDICATIONS	ABORTED		STERILIZED		NOT STERILIZED
Tuberculosis	32		19		13
Pulmonary		29		17	12
Other		3		2	1
Heart Disease	27		24		3
Rheumatic heart disease		25		22	3
Other		2		2	0
Nephritis	22		10		12
Chronic		19		10	9
Other		3		0	3
Other Toxemias	15		7		8
Hypertension		7		6	1
Pre-eclampsia		2		1	1
Hyperemesis		6		0	6
Neurologic and Psychiatric	20		15		5
Psychosis and psychoneurosis		10		5	5
Epilepsy		4		4	0
Multiple sclerosis		3		3	0
Other		3		3	0
Miscellaneous	18		15		3
Arthritis		5		5	0
Pyelitis and pyelonephritis		3		2	1
Blood dyscrasias		4		2	2
Diabetes		2		2	0
Fibroids		2		2	0
Other		2		2	0
Total	134		90		44

The largest group comprises patients with tuberculosis (Table II) of all types. Twenty-nine of these women had pulmonary tuberculosis; in addition, 2 had cardiac lesions, 1 had bilateral bronchiectasis, and 1 had fibroids. Three women had tuberculosis of the spine, intestines, and lymph nodes, respectively. It is significant that of the 19 women who were sterilized at the time the pregnancy was interrupted, all but 3 had at least one living child at the time of the abortion; 5 had 2; 4 had 3; 3 had 4, and 1 had 6. On the other hand, among 13 women who were aborted but not sterilized, only 4 had a living child. It is hard to escape the conclusion that strict attention to the medical problem, without reference to the number of children already in the family, might have led to different recommendations in some of these cases. Most of the patients were apparently benefited; 3 were probably not. The only technical accident in the entire series of 134 interruptions occurred in one of these 3 patients. She developed an evagination following a hysterectomy, but recovered. One patient who declined sterilization at the time of her abortion in 1935 came back pregnant in 1936 and refused interruption, carrying her fetus to delivery at term. She was sterilized the following year, and has been in fair health since.

It is well established that cardiac disease is never benefited by pregnancy, labor, and the puerperium. Some patients have considerable cardiac embarrassment, and a small number decompensate and die in the puerperium. Nevertheless, only 5 out of the 27 patients (Table III) were without living children. Rheumatic heart disease was present in 25 of the 27 cases. The results from those followed include 13 satisfactory, 2 unchanged, and 1 unsatisfactory. All but 3 were sterilized (one of these refused). In contrast to the fact that no fatalities occurred in this series of women with severe cardiac lesions, 8 deaths resulted in the same period among patients with heart disease who carried a pregnancy to viability. Surely then therapeutic abortion rendered a valuable service by shielding the heart from a heavier burden and at the same time prolonging the

the perpetuation of serious hereditary defects. It is obvious that consultation with experts in the fields concerned is highly desirable.

The consultants should state definitely (1) whether the pregnancy should continue or be interrupted, and (2) whether future childbearing would be approved or prevented. Naturally, one should be reluctant to interrupt a pregnancy for a condition which makes childbearing hazardous and yet leave the woman exposed to the danger of further gestations or repeated abortions. On the other hand, there are various maternal disorders, such as hyperemesis gravidarum and certain types of tuberculosis, which may not in themselves constitute a bar to a future pregnancy, though they may at times be an urgent indication for termination of the current one. Likewise, there are occasional pregnant women so desperately ill as to require abortion with a minimum of trauma, and in such individuals the problem of limiting childbearing in the future may be left for later consideration.

A patient may refuse sterilization, yet agree to the termination of the pregnancy. Under such circumstances it has been our general policy to decline to interfere because of the likelihood that the problem will develop again. In our series of 134 therapeutic abortions, a sterilizing procedure was done on the mother in 90 cases, or 67 per cent, and on the husband in 3 cases, or 2 per cent; in only two cases where sterilization was recommended by the consultant but refused by the patient was a therapeutic termination carried out, and one of these individuals refused sterilization twice (Cases 2 and 3, Table IV).

#### DATA

Table I lists the major groups, the respective indications, and the number of sterilization operations in each.

Thoroughly adequate follow-up in our cases has not always been possible. One would like to know how the patient reacted to the interruption of her pregnancy, not only within the first weeks or months, but over a period of years. Since the majority of the terminations were done for medical rather than obstetric reasons, the patients have been followed by various clinics and specialists. Some of the patients with tuberculosis, for example, went to sanatoria; others returned to Board of Health out-patient clinics; several did not return to our own clinic for their scheduled check-up. Among the cardiac patients, the contact with the medical clinic was generally kept up over a longer period, and the same remark can be made concerning the nephritis and hypertension groups. In the whole series, 51 patients were followed for periods longer than a year; 21 for at least three years; 10 for from five to eight years.

An attempt has been made, however, to make an unbiased decision in each case as to whether, in retrospect, the procedure was wisely chosen, and whether the immediate and remote effects justified the expectation that it would improve the health and prolong the life of the mother. This impression has been recorded in the tables under the heading of "results," where the outcome is arbitrarily designated as "satisfactory" (adequate follow-up, with improvement in the patient's health attributable to the therapeutic abortion); "unchanged" (adequate or partial follow-up, with negligible improvement in the patient's health); "unsatisfactory" (procedure failed to accomplish what was intended); and "undetermined" (insufficient data for deciding on the appropriateness or effectiveness of the procedure).

TABLE III. THERAPEUTIC ABORTION IN 27 CASES OF HEART DISEASE

NO.	UNIT NO.	AGE	GRAV.	LIVING CHILD.	DIAGNOSIS	WEEKS PREG-NANT	TERMINATION	STERIL.	RESULTS
1	74280	23	i	0	R.H.D.* Mit. & aort. insuf. & sten.	10	D & C*	No	Undetermined
2	181401	25	ii	0	R.H.D. Mit. & aort. insuf.	8	D & C	No	Undetermined
3	63319	30	iv	1	R.H.D. Mit. sten.	6	D & C	No	Undetermined
4	60021	18	ii	0	R.H.D. Mit. sten.	12	Abd. hysterot.	Yes	Undetermined
5	70412	21	iii	2	R.H.D. Mit. & aort. insuf.	6	Abd. hysterot.	Yes	Undetermined
6	103353	22	iii	2	R.H.D. Mit. sten.	16	Abd. hysterot.	Yes	Undetermined
7	45955	24	iv	2	R.H.D. Mit. sten. & insuf.	16	Abd. hysterot.	Yes	Satisf., prev. ces. sec.
8	80861	25	ii	1	R.H.D. Mit. sten. & insuf.	12	Abd. hysterot.	Yes	Satisfactory
9	24818	25	iii	2	R.H.D. Mit. sten. & insuf.	12	Abd. hysterot.	Yes	Satisfactory
10	188836	26	ii	1	R.H.D. Mit. sten. & insuf.	14	Abd. hysterot.	Yes	Satisfactory
11	121844	27	iii	2	R.H.D.	10	Abd. hysterot.	Yes	Satisf., prev. ces. sec.
12	129181	28	i	0	R.H.D.	12	Abd. hysterot.	Yes	Satisfactory
13	75091	28	iv	2	Mit. stenosis	11	Abd. hysterot.	Yes	Undetermined
14	64157	29	iv	2	Mit. stenosis & insuf.	12	Abd. hysterot.	Yes	Satisfactory
15	80130	29	iii	2	Mit. stenosis prev. decomp.	22	Abd. hysterot.	Yes	Satisfactory
16	50187	30	ii	1	Mit. stenosis & insuf. decomp.	10	Abd. hysterot.	Yes	Satisfactory
17	136490	31	iii	2	comp.	17	Abd. hysterot.	Yes	Unsatisf., prev. ces. sec.
18	99028	33	viii	2	R.H.D. Mit. insuf.	16	Abd. hysterot.	Yes	Undetermined
19	153006	34	vi	2	R.H.D. Mit. sten. vascul. renal d.	10	Abd. hysterot.	Yes	Undetermined
20	107894	38	iii	1	R.H.D. Mit. sten.	16	Abd. hysterot.	Yes	Unchanged
21	159341	38	v	4	R.H.D. Mit. sten. & insuf.	9	Abd. hysterot.	Yes	Satisfactory
22	46278	25	iii	2	R.H.D. Mit. sten. prev. decomp.	12	Abd. hysterot.	Yes	Satisfactory
23	46278	26	iv	2	R.H.D. Mit. sten. prev. decomp.	24	Abd. hysterect.	Yes	Satisfactory
24	99382	33	viii	4	R.H.D. Mit. sten. prev. decomp.	6	Abd. hysterect.	Yes	Unchanged
25	38927	35	xiii	5	R.H.D. Mit.	8	Abd. hysterect.	Yes	Satisfactory
26	133261	21	i	0	Myocarditis, aortic insuf.	12	Abd. hysterect.	Yes	Undetermined
27	105821	25	iii	2	Myocarditis, coarctation aorta	12	Abd. hysterot.	Yes	Undetermined

\*R.H.D., rheumatic heart disease; D &amp; C, dilatation and curettage.

TABLE II. THERAPEUTIC ABORTION IN 32 CASES OF TUBERCULOSIS

NO.	UNIT NO.	AGE	GRAV.	LIVING CHILD.	DIAGNOSIS	WEEKS PREG-NANT	TERMINATION	STERIL.	RESULTS
1	115152	20	i	0	Tuberc. pulmon.	6	D & C	No	Unchanged
2	91089	21	ii	1	Tuberc. pulmon.	12	D & C	No	Satisf. Term deliv. later
3	183128	23	i	0	Tuberc. pulmon.	8	D & C	No	Satisf. Term deliv. later
4	199278	23	ii	1	Tuberc. pulmon.	8	D & C	No	Undetermined
5	74303	23	ii	1	Tuberc. pulmon.	8	D & C	No	Undetermined
6	51888	24	i	0	Tuberc. pulmon.	6	D & C	No	Satisfactory
7	62230	24	i	0	Tuberc. pulmon.	8	D & C	No	Unchanged
8	2818	29	v	2	Tuberc. pulmon.	6	D & C	No	Satisfactory
9	117606	29	ii	0	Tuberc. pulmon.	12	D & C	No	Undetermined
10	126718	29	ii	0	Tuberc. pulmon.	10	D & C	No	Undetermined
11	160053	25	i	0	Tuberc. pulmon.	16	Bag. induct. & embry.	No	Unsatisfactory
12	111644	21	v	0	Tuberc. pulmon.	12	Abd. hysterot.	Yes	Unchanged
13	172584	22	vi	1	Tuberc. pulmon.	12	Abd. hysterot.	Yes	Undetermined
14	87569	26	ii	4	Tuberc. pulmon.	14	Abd. hysterot.	Yes	Unchanged
15	53323	27	iii	2	Tuberc. pulmon.	10	Abd. hysterot.	Yes	Undetermined
16	163698	28	xi	0	Tuberc. pulmon.	12	Abd. hysterot.	No	Undetermined
17	89994	30	vi	2	Tuberc. pulmon.	14	Abd. hysterot.	Yes	Satisfactory
18	44884	31	vii	3	Tuberc. pulmon.	11	Abd. hysterot.	Yes	Undetermined
19	67838	32	vii	6	Tuberc. pulmon.	12	Abd. hysterot.	Yes	Undetermined
20	123909	34	viii	3	Tuberc. pulmon.	14	Abd. hysterot.	Yes	Satisfactory
21	128294	35	i	0	Tuberc. pulmon.	8	Abd. hysterot.	Yes	Undetermined
22	135893	36	ii	0	Tuberc. pulmon.	16	Abd. hysterot.	Yes	Unsatisfactory
23	145045	40	ii	Twins	Tuberc. pulmon.	9	Abd. hysterot.	Yes	Unchanged
24	149491	40	v	4	Tuberc. pulmon.	16	Abd. hysterot.	Yes	Satisfactory
25	128644	43	vi	3	Tuberc. pulmon.	17	Abd. hysterot.	Yes	Unchanged
26	83109	29	iv	3	Tuberc. pulmon.	14	Abd. hysterot.	Yes	Undetermined
27	58116	34	iii	1	Tuberc. pulmon.	14	Abd. hysterect.	Yes	Satisfactory
28	111639	34	vi	4	Tuberc. pulmon.	12	Abd. hysterect.	Yes	Undetermined
29	141204	39	v	2	Tuberc. pulmon.	6	Abd. hysterect.	Yes	Unchg. Evisceration
30	117364	22	i	0	Tuberc. intest.	6	D & C	No	Undetermined
31	41238	20	ii	1	Tuberc. vert. ment. defect.	10	Abd. hysterot.	Yes	Satisfactory
32	79710	29	iv	2	Tuberc. lymphat.	10	Abd. hysterot.	Yes	Satisfactory

\*R.H.D., rheumatic heart disease; D. &amp; C., dilatation and curettage.

TABLE V. THERAPEUTIC ABORTION IN 15 CASES OF HYPERTENSION, PRE-ECLAMPSIA AND HYPEREMESIS

NO.	UNIT NO.	AGE	GRAV.	LIVING CHILD.	DIAGNOSIS	WEEKS PREG-NANT	TERMINATION	STERIL.	RESULTS
1	46402		viii	0	Hyperten., obesity	8	D & C*	No	Satisfactory
2	130528	23	ii	0	Hyperten., C.N.S.* syphilis	12	Abd. hysterot.	Yes	Undetermined
3	91383	24	ii	1	Hyperten.	6	Abd. hysterot.	Yes	Undetermined
4	193754	34	iii	2	Hyperten.	13	Abd. hysterot.	Yes	Satisfactory
5	173033	35	vii	0	Hyperten., fibroids	18	Abd. hysterect.	Yes	Unchanged
6	58806	36	ii	1	Hyperten.	10	Abd. hysterect.	Yes	Unchanged
7	133775	42	v	4	Hyperten.	17	Abd. hysterect.	Yes	Unchanged
8	142389	25	i	0	Pre-eclampsia	22	Vag. hysterot. & embryot.	No	Satisfactory
9	143069	37	iv	3	Pre-eclampsia	10	Vag. hysterect.	Yes	Unchanged
10	195680	23	ii	0	Hyperemesis	8	D & C	No	Satisfactory
11	117960	25	iii	1	Hyperemesis	12	D & C	No	Satisf. Term preg. later
12	63614	29	ii	1	Hyperemesis, hyperthyr.	10	D & C	No	Undetermined
13	5007	34	ii	1	Hyperemesis	10	D & C	No	Satisfactory
14	121850	32	iii	1	Hyperemesis	14	Vag. hysterot.	No	Unsatish. Died 33 hr.
15	145144	23	i	0	Hyperemesis	20	Vag. hysterot.	No	Satisfactory

\*C.N.S., central nervous system; D &amp; C, dilatation and curettage.

TABLE IV. THERAPEUTIC ABORTION IN 22 CASES OF NEPHRITIS

NO.	UNIT NO.	AGE	GRAV.	LIVING CHILD.	DIAGNOSIS	WEEKS PREG-NANT	TERMINATION	STERIL.	RESULTS
1	54752	18	ii	1	Chr. nephritis	8	D & C	No	Undetermined
2	89797	20	i	0	Acute nephritis	22	Gauze induct. embry.	No	Unchanged
3	89797	23	ii	0	Chr. nephritis	8	D & C	No	Unchanged
4	126939	20	i	0	Subacute nephritis	18	D & C & embry.	No	Unchanged
5	143071	33	x	3	Chr. nephritis, hyperten.	6	D & C	No	Undetermined
6	64538	34	iv	2	Chr. nephritis	6	D & C	No	Undetermined
7	47832	36	ix	9	Chr. nephritis	8	D & C	No	Unsatisf., died 7 mo.
8	107854	40	iii	2	Chr. nephritis	8	D & C	No	Satisfactory
9	71202	42	iv	2	Chr. nephritis	8	D & C	No	Undetermined
10	127581	20	i	0	Subacute nephritis	16	Vag. hysterect. & embry.	No	Unchg., died 2½ yr.
11	156261	20	i	0	Chr. nephritis	21	Vag. hysterect.	No	Unsatisf., died 1 yr.
12	68801	36	v	0	Chr. nephritis	26	Vag. hysterect. & embry.	No	Undetermined
13	138958	20	iii	2	Chr. nephritis	10	Abd. hysterot.	Yes	Satisfactory
14	93989	21	iii	0	Chr. nephritis	24	Abd. hysterot.	Yes	Satisfactory
15	161815	23	ii	1	Chr. nephritis, hyperthy.	14	Abd. hysterot.	Yes	Satisfactory
16	39070	31	v	2	Chr. nephritis	10	Abd. hysterot.	Yes	Undetermined
17	180480	33	xi	9	Chr. nephritis	24	Abd. hysterot.	Yes	Unchanged
18	121529	34	ii	0	Chr. nephritis, fibroids	14	Abd. hysterot.	Yes	Satisfactory
19	59559	34	viii	3	Chr. nephritis	16	Abd. hysterot.	Yes	Satisfactory
20	51010	36	v	4	Chr. nephritis, hyperthy.	24	Abd. hysterot.	Yes	Undetermined
21	114323	42	vii	5	Chr. nephritis	20	Abd. hysterect.	Yes	Unchanged
22	83430	43	xvi	13	Chr. nephritis	12	Abd. hysterect.	Yes	Unchanged

TABLE VII. THERAPEUTIC ABORTION IN 18 CASES OF MISCELLANEOUS DISORDERS

NO.	UNIT NO.	AGE	GRAV.	LIVING CHILD.	DIAGNOSIS	WEEKS PREG-NANT	TERMINATION	STERIL.	RESULTS
1	23004	29	ii	1	Arthritis deformans, R.H.D.	8	Abd. hysterot.	Yes	Unchanged
2	42889	29	iii	2	Arthritis deformans	8	Abd. hysterect.	Yes	Undetermined
3	93997	34	iv	2	Arthritis deformans	7	Abd. hysterect.	Yes	Undetermined
4	86487	39	ii	1	Arthritis deformans	8	Abd. hysterect.	Yes	Undetermined
5	20354	39	iii	2	Sacroiliac arthritis	12	Abd. hysterect.	Yes	Satisfactory
6	75446	28	iii	1	Pyelitis	6	D & C	No	Undetermined
7	84984	35	iv	2	Pyelitis, hydronephrosis	7	Abd. hysterot.	Yes	Satisfactory
8	142382	20	ii	1	Pyelonephritis	12	Abd. hysterot.	Yes	Unchanged
9	1312	34	i	0	Diabetes mellitus, fibroids	10	Abd. hysterect.	Yes	Unchanged
10	177505	36	iii	1	Diabetes mellitus	12	Abd. hysterot.	Yes	Undetermined
11	122963	33	iii	1	Purpura, hypercemesia	6	D & C	No	Undetermined
12	43089	24	iv	2	Purpura	17	Abd. hysterect.	Yes	Undetermined
13	71865	41	vi	5	Anemia, secondary unresponsive	10	D & C	No	Undetermined
14	59215	26	ix	6	Hodgkins' dis., failed x-ray steril.	18	Abd. hysterot.	Yes	Unchanged
15	69839	34	i	0	Uterine fibroid, choc. cyst	10	Abd. hysterect.	Yes	Undetermined
16	111614	37	i	0	Uterine fibroid	8	Abd. hysterect.	Yes	Undetermined
17	39680	30	ix	6	Arsenical hepatitis, syphilis	10	Abd. hysterot.	Yes	Satisfactory
18	64133	28	iii	2	Bronchiectasis	14	Abd. hysterot.	Yes	Unchanged

TABLE VI. THERAPEUTIC ABORTION IN 20 CASES OF NEUROLOGIC AND PSYCHIATRIC DISEASES

NO.	UNIT NO.	AGE	GRAV.	LIVING CHILD.	DIAGNOSIS	WEEKS PREG-NANT	TERMINATION	STERIL.*	RESULTS
1	189310	34	v	3	Psychosis, hyperemesis	7	D & C	No H	Undetermined
2	135235	35	iii	2	Psychosis	10	D & C	No H	Undetermined
3	51096	38	ii	0	Psychosis familial (husband)	7	D & C	No H	Undetermined
4	100903	26	ii	1	Psychosis, hyperemesis	26	Vag. hysterot.	No	Undetermined
5	210908	31	iii	2	Psychosis, syphilis	12	Abd. hysterot.	Yes	Unchanged
6	107065	32	iv	2	Psychosis, hyperemesis	14	Abd. hysterot.	Yes	Undetermined
7	188891	27	iii	2	Psychosis (post partum twice)	16	Abd. hysterect.	Yes	Satisfactory
8	99791	32	iii	2	Psychoneurosis, hyperemesis	10	D & C	No	Undetermined
9	48434	31	ii	0	Psychoneurosis	8	Abd. hysterot.	Yes	Satisfactory
10	3004	37	vi	5	Psychoneurosis	10	Abd. hysterot.	Yes	Satisfactory
11	73754	20	ii	1	Epilepsy	14	Abd. hysterot.	Yes	Unchanged
12	145315	23	i	0	Epilepsy	12	Abd. hysterot.	Yes	Unchanged
13	79284	27	ii	1	Epilepsy	22	Abd. hysterot.	Yes	Unchanged
14	115826	31	ii	1	Epilepsy	12	Abd. hysterect.	Yes	Undetermined
15	46438	24	ii	1	Multiple sclerosis	14	Abd. hysterot.	Yes	Undetermined
16	127905	26	iii	1	Multiple sclerosis	8	Abd. hysterot.	Yes	Unchanged
17	99905	32	iv	3	Multiple sclerosis	12	Abd. hysterot.	Yes	Unchanged
18	35859	40	iii	2	Otosclerosis	10	Abd. hysterot.	Yes	Unchanged
19	166611	28	iii	2	Meningoencephalitis	12	Abd. hysterot.	Yes	Undetermined
20	48654	34	viii	2	Pituitary tumor, acromegaly	12	Abd. hysterot.	Yes	Unchanged

\*No H, husband only sterilized.



4. It is rarely, if ever, an emergency procedure, and should not be undertaken until the patient is in the best possible condition for it.

5. It is not without some risk of operative complications, and even fatality.

6. Sterilization is indicated whenever the same problem would arise in a subsequent pregnancy.

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#### DISCUSSION

DR. JOHN H. MOORE, GRAND FORKS, N. D.—Our series of 19 therapeutic abortions was done for the following conditions: nephritis, 6 cases; hydronephrosis, 1 case; pulmonary tuberculosis, 4 cases; hyperemesis gravidarum, 3 cases; hypertension, 2 cases; mitral stenosis, 1 case; gestational psychosis, 1 case; myomatous uterus, 1 case.

I am fully in accord with Dr. Hesseltine's statement that medical indications only should indicate the performance of therapeutic abortion and then only after competent and careful consultation, when all other therapy has failed.

In our 19 therapeutic abortions, hysterotomy and sterilization was done in 11; subtotal abdominal hysterectomy in 1 and dilatation and curettage in 7. In 2 of the patients upon whom dilatation and curettage was employed, we had recommended hysterotomy and sterilization, but permission was refused. Thus there were 14 of the 19 patients whose medical condition was such that we believed future childbearing would be hazardous to life. In other words, 73 per cent of this series required sterilization as well as therapeutic abortion. The actual percentage sterilized was 63 per cent.

In our series there was only one primiparous patient, an advanced case of pulmonary tuberculosis with marked cavitation; all of the other patients had from 2 to 7 living children with the exception of one of the patients with hypertension, who had had a therapeutic abortion elsewhere by dilatation and curettage in her first pregnancy.

What is the salvage rate in patients upon whom therapeutic abortion is done? While there was no mortality from the surgical procedures in my series, a follow-up of these 19 patients has shown that 4 of them died from two to five years after the therapeutic abortion from the medical condition which indicated the abortion, a delayed mortality of 22 per cent. Two of the remaining, living patients are hopeless invalids.

The problem of therapeutic abortion is a medical one. We should not be led astray by a confusion of religious, sociologic or economic reasons for or against it. The medical conditions present in any case where this operation is under serious consideration will be sufficient to tax all of our diagnostic, prognostic, and therapeutic abilities.

patient's life. Termination of pregnancy before viability is indicated only when response to therapy and management fail to arrest the downward course of the heart disease or when there is inadequate response to therapy in the advanced stages.

That pregnancy and nephritis are often incompatible has long been established (Table IV). Only 13 of 22 nephritic patients were known to have living children. Twelve of the 22 were not sterilized because of the poor prognosis for life and the unlikelihood of subsequent gestations. Termination of pregnancy was of value in removing the additional burden upon the vascular and renal systems. Two patients appear not to have benefited, 9 were not followed, 6 had a satisfactory response, and 5 remained unchanged.

Among 7 hypertension patients (Table V), 2 had no follow-up, 2 were benefited, and 3 remained unchanged. One of the 2 pre-eclamptic patients had a persistent hypertension, while the other one apparently was free from residual damage. The only immediate fatality in the entire series of 134 cases occurred in the hyperemesis group. This patient had been under care elsewhere for almost three months. Her condition was critical on admission, and supportive treatment was unavailing. The termination was undertaken even though the outlook was grave, as all other measures had failed. She died thirty-three hours after the operation. Of the other patients, one did not return and the remaining 4 had completely satisfactory results. One patient went through pregnancy and normal labor subsequently.

The neurologic and psychiatric disorders (Table VI) comprise 7 psychoses, 3 psychoneuroses, 4 epilepsies, 3 multiple scleroses, and one each of otosclerosis, meningoencephalitis, and pituitary tumor. Sterilization operations were performed on 15 patients and on the husbands of 3 others. The ultimate results are undetermined in 10, unchanged in 6, satisfactory in 3, and unsatisfactory in 1. The six patients whose condition is classified as unchanged probably derived benefit from the interruption; the complicating disorder at least did not progress as rapidly as it might have in the presence of the continuing pregnancy. Case 3 indicated a problem in which insanity has been transmitted directly and consecutively through at least 3 generations of the husband's family. The outlook for this child on a basis of his family tree was indeed tragic.

Table VII presents a group of miscellaneous disorders. The fact that only 3 patients with pyelitis and 2 with diabetes required therapeutic abortion indicated the infrequency of the procedure in such conditions. The 5 cases of arthritis were interrupted because the disease progressed distinctly more rapidly during pregnancy.

#### SUMMARY

In retrospect, it appears that all of the terminations were undertaken after adequate observation and thorough consideration. In spite of this caution, certain of the abortions failed to give the expected benefit, and did not relieve the underlying disorder. In a few cases the interruptions were probably delayed too long. On the whole, it seems clear that considerably more good was accomplished than is indicated by the arbitrary designations in the result columns.

A number of conclusions may be drawn:

1. Therapeutic abortion is a necessary, but relatively infrequent, obstetric procedure.
2. It should be done only to save or to prolong significantly the life of the mother, or to prevent the transmission of serious hereditary defects.
3. It should be attempted only after adequate consultation, only in reputable hospitals, only by competent operators, and only after both the husband and wife (or legal guardian) consent.

# A STUDY OF THE POSSIBLE SIGNIFICANCE OF THE VAGINAL SMEAR AS AN ADDITIONAL FACTOR IN THE DIAGNOSIS OF INCOMPLETE ABORTION\*

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HUMAN vaginal smears have been used for many years in the study of various conditions but their application to morphologic and physiologic studies had been extremely limited until the last twelve or fifteen years. The role, if any, that the vaginal smear is to play as a diagnostic help in clinical medicine has only been suggested and that by not more than three investigators to date. The work done so far enables us to test the adaptability and significance of the vaginal smear as a useful clinical procedure. The object of this work has been to study the vaginal smear and its possible significance as an additional factor in the diagnosis of incomplete abortion, and to develop a staining technique that is sufficiently simple to be applicable to office and clinic use.

## REVIEW OF LITERATURE

Dierks tried to show that in the human female a definite cycle takes place in the vagina. At the height of the change the epithelium is composed of three layers: a basal or deep, a functional or superficial, and an intra-epithelial or cornified layer situated between the first two. Adler agreed with Dierks after finding evidence of three layers to be most marked during the premenstrual period. He further pointed out the presence of an exceedingly well-developed functional layer in early pregnancy. He found no evidence of a functional layer in the post-partum period, during lactation, after the menopause and before puberty. This fact strengthens the belief in a vaginal cycle and tends to corroborate the contention of Dierks, that the vaginal cycle keeps pace with the cycle of the uterus and ovary.

In 1925, Papanicolaou announced in a preliminary report some of the results of his early human vaginal smear studies. He maintained that pregnancy, among other things, affects the entire genital tract, including the vagina, in a way which produces definite and typical changes in the consistency and make up of the vaginal smear.

Kelly, in developing a technique for the diagnosis of pregnancy in the guinea pig by a study of the vaginal epithelium, observed that certain changes are quite marked. They begin to develop in the second week and are well developed by the end of the third week. These changes may persist for at least two or three weeks following delivery estrus.

After a study of large numbers of vaginal smears from different mammals, Papanicolaou states that he has been led to realize that pregnancy, as well as different pathologic conditions of the ovaries and genital tract, might be diagnosed more or less accurately by an analysis of such smears. The entire composition of the vaginal smear changes rather typically under different conditions.

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DR. M. W. SEARIGHT, MEMPHIS, TENN.—We have worked out a plan for a rapid sterilization. A transverse incision is made, 4 cm. long and 6 cm. above the symphysis pubis. With the patient in the Trendelenburg position a ribbon retractor is run into the cul-de-sac. The assistant pushes against the cervix and the uterus is brought into the small opening. Sterilization can be carried out without danger, and you can suspend the uterus at the same time if it is necessary. These patients are able to leave the hospital in five days. We have had no complication following this operation. It is much quicker than the vaginal route, and there is no stretching of the ligaments as occurs after the vaginal operation.

DR. ALBERT E. CATHERWOOD, DETROIT, MICH.—Michigan is one of 38 states in which the indication for therapeutic abortion is solely that of saving the life of the mother. Formerly it was not difficult for any one who wanted to do a therapeutic abortion to get one or two doctors to agree with him.

We have set up a permanent therapeutic abortion committee in the Harper Hospital which considers all cases in which therapeutic abortion may be indicated. The case is thoroughly studied and presented by the man who has worked it up. The committee then considers what action should be taken, not only whether or not therapeutic abortion should be done but also the question of sterilization. We think it a very satisfactory method, and have noted that since the appointment of this permanent committee, the number of therapeutic abortions in Harper Hospital has been greatly reduced.

DR. FREDERICK H. FALLS, CHICAGO, ILL.—To the Research Hospital of the University of Illinois a good many patients are sent by the Chicago Municipal Tuberculosis Sanitarium staff for therapeutic abortion. We do not as a rule accept the judgment of those men who have had a good deal of special training in tuberculosis unless the medical consultants in the University of Illinois agree with them. Williams showed that those patients that were aborted from his clinic did worse than those that were not aborted.

I doubt very much whether psychosis is ever an indication for abortion. The psychosis that occurs in pregnancy is not due to the pregnancy. The pregnancy is only the straw that breaks the camel's back, and the pregnant woman who is psychotic will not be helped by abortion. The baby has a right to its existence and should have its chance. The possibility of its being psychotic is not 100 per cent by any means.

Vaginal sterilization is a very valuable way of sterilizing women whom the medical complication makes poor surgical risks. This can be done under local anesthesia up to the third or fourth month. I believe that is the best way to do it.

DR. ROBERT M. GRIER, EVANSTON, ILL.—It has been the experience of Dr. Don Sutton in his large heart clinic at the Cook County Hospital, where he has handled and followed many women with rheumatic heart disease during pregnancy, that this condition is rarely ever an indication for therapeutic abortion. He and others recently reported a large series of patients who were carried through pregnancy and labor, with but one death. Many of these women were decompensated at some time during their pregnancy but with proper management were able to be made to compensate before delivery.

DR. HESSELTINE (closing).—The therapeutic abortion committee mentioned by Dr. Catherwood is a very good idea. It would give moral support and medico-legal protection to the institution and to the individuals responsible.

Dr. Grier brought out a very good point about heart disease. We did not have a single fatality in a fairly large series of 27 cases. These were not mild cases, but practically all had decompensation or well-advanced heart disease.

It is well to remember that in certain diseased conditions the fetus may suffer appreciably. That is not a direct indication, but it does enter into consideration. At the same time there may be severe damage to the mother, as for instance in nephritis.

Smith describes the outer layer or superficial zone as made up of squamous cells containing small dark-staining nuclei and clear-staining cytoplasm. They are flat, elliptical or elongated and are several layers thick.

The middle layer called the intraepithelial or cornified zone is differentiated from the outer by slightly expanded pale cells that vary somewhat in size but are definitely larger and paler staining. They undergo cornification changes which are manifest by a marked cellular flattening and the development of pyknotic nuclei.

The deep layer or basal zone is composed of a basement membrane made up of two or three layers of dark-staining cells, having darker-staining nuclei and relatively little cytoplasm. Immediately above this are located several layers of increasingly larger cells whose size is due to an increase in the amount of cytoplasm. They tend toward the round, elliptical and cuboidal forms and as they



Fig. 1.—Normal vaginal epithelium (courtesy of Dr. M. A. Roblee). 1, Superficial zone; 2, intraepithelial zone; 3, outer basal zone; 4, inner basal zone; B, basement membrane.

approach the intraepithelial and superficial layers they begin to flatten out consistently. This tendency is not quite as marked, however, as in the cells of the more superficial layers. They are consistently smaller in size. This feature makes identification of this layer relatively easy.

Papanicolaou recognizes these epithelial zones but feels that while a study of the vaginal mucosa in sections does not justify a division of the basal layer into an inner and outer basal zone, a study of the cells themselves as found in the vaginal smear warrants this further division into an inner basal or germinative zone and an outer basal or pavement cell zone. The necessity for this is the fact that during the post-partum period cells corresponding to those from a well-differentiated outer basal, or pavement cell zone, appear in abundance.

So far as we have been able to determine, this particular type of cell (pavement cell) does not characterize any other type of gynecologic

The occurrence of pregnancy may be definitely recognized by certain typical changes in the structure of the smear. The prevailing types of desquamated cells show a deviation from the usual types. Soon after the beginning of pregnancy there is a distinct tendency for cells to assume certain characteristic forms. These forms may appear, occasionally, in other conditions normal or otherwise but are not so typical or as consistent as in the pregnancy smear.

Papanicolaou says, "The approach or occurrence of parturition, abortion or resorption may possibly be revealed by certain smear changes. As soon as delivery or abortion takes place and the corpus luteum begins to regress, the smear presents an entirely different appearance indicating the onset of active destructive processes." He believes that as a whole the study of the vaginal smear seems to be of important diagnostic value and may be a useful adjunct in gynecology in the diagnosis of certain doubtful cases.

#### VAGINAL SMEARS IN ABORTIONS

With this in mind and aware of the frequency with which the gynecologist is confronted with patients whose chief complaint is abnormal vaginal bleeding, and because incomplete abortion is generally recognized as the most common cause of this bleeding, it was decided to undertake this investigation to see whether or not a vaginal smear procedure sufficiently simple to be applicable for clinic or office use, might be recognized or developed; moreover if its dependability could be established to a degree of satisfaction that would warrant the general recognition of the vaginal smear as a useful adjunct in the diagnosis of incomplete abortion.

#### THE HISTOMORPHOLOGY OF THE VAGINAL EPITHELIUM AS THE BASIS OF THE VAGINAL SMEAR

In order to explain the probable source of origin of cells that characterize the smear of incomplete abortion, a discussion of the histologic aspects of the vaginal mucous membrane is essential.

The reason for the presence of cells in the vaginal smear has been very satisfactorily explained by Papanicolaou.<sup>16</sup> He says: "Most of the cells found in the vaginal smear are derived from the superficial layers of the vaginal epithelium. These cells are subject to continuous desquamation and are constantly present in the vaginal canal. Cells of the deeper layers are less frequently thrown off and appear in large quantities only when active denudation follows periods of excessive growth. This occurs in humans after parturition."

Stieve found a marked increase in the height of the vaginal epithelium in the premenstrual phase of the human menstrual cycle, but this is not as extensive as the increase which occurs during the first months of gestation. The proliferation taking place in early pregnancy is from the basal, or germinative, layer. It results in a gradual increase in the number of epithelial cells and cell layers. The cells themselves and their nuclei are noticeably increased in size. After the onset of parturition, degenerative changes set in and result in an extensive desquamation of all cellular excess.

Smith studied this problem on sections taken at autopsy. He also noted and described three layers in the vaginal mucosa. Because of its completeness and relative simplicity, his description has been chosen as a part of this paper. It has been, for the most part, the histologic basis upon which our study of the contents of the vaginal mucosa has been made. We have also taken into consideration the additional division of the basal layer as described by Papanicolaou (Fig. 1).

available for study and comparison. These were prepared for a study of another phase of the vaginal smear problem. In one of these cases conception took place about the middle of the second month and daily smears were continued for the next three weeks.

Each of these series was first studied separately and individual characteristics noted. Then comparisons with our slides were made. They were carefully studied and worked out in an endeavor to recognize any morphologic characteristics that might consistently identify the vaginal smear of incomplete abortion.

In the collection of these slides care was taken to make three or four each time so as to have available practically identical smears for staining with the various types of procedures used.

For controls, smears taken during the premenstrual and menstrual phases of apparently normal cycles were used; also, those prepared from all pregnancy and post-partum cases studied in this series.

#### DESCRIPTION OF VAGINAL SMEAR CHANGES NOTED IN PROVED CASES OF INCOMPLETE ABORTION

Although our series of cases of incomplete abortion is relatively small, we feel, after repeated examination and careful study of the various types of cells contained in these smears, that we have been able to recognize sufficient morphologic changes to warrant publication of these findings as a preliminary report. It is not our intention at this time to try to establish these characteristics as definite vaginal smear signs of incomplete abortion. Our present series of cases is too small to do this, even though the following changes were observed regularly and consistently in almost every smear studied.

a. Superficial and intraepithelial cells are present in relatively small numbers and are about normal in size with small dark staining or pyknotic nuclei and homogenous pale blue staining cytoplasm. Occasionally we noticed the relative increase in size of the nucleus as seen in pregnancy smears. These cells are irregular in shape and may be fragmented, compressed or folded to a greater extent than in the menstrual smear and to a less extent than in the smears of early or late pregnancy. They correspond fairly well to those seen in post-partum smears.

b. Outer basal or pavement cells (Fig. 3) are present in sufficient numbers to cause them to be an easily recognized characteristic of the incomplete abortion smears. They are in general equally or more numerous than the superficial cells. Their nuclei are large in proportion to the cytoplasm, more so than is observed in the superficial cells in pregnancy smears. They stain a medium blue color with a pinkish tinge. They always take a darker stain than the cytoplasm, but the contrast is not as marked as in the superficial cells.

The cytoplasm is clear and homogenous but may contain a few fine granules. It may be definitely cornified, but the majority of cells show only partial cornification.

In size they are smaller than the superficial type. It is not unusual for them to be only half or two-thirds as large. The ratio of total nuclear to total cytoplasmic substance is about one to two, as a rule. This seems to be due to a decrease in size of the cell rather than to an increase in size of the nucleus. Papanicolaou described these cells only in post-partum and postmenopausal smears.

c. Inner basal or germinative cells (Fig. 2) are consistently also present in smears of incomplete abortion. They can be recognized easily, but were not readily identified at first because of their marked scarcity in all other types of vaginal smears studied. They are slightly smaller than the outer basal type, have a homogenous, medium to light blue-staining cytoplasm and a relatively

condition. *Since they abound in the average post-partum smear, it seemed reasonable to us to assume that their presence in vaginal smears taken from women suspected of having an incomplete abortion, might be acceptable as a diagnostic feature of this condition.* Hence, part of our endeavor has been to try to determine whether or not the absence of pavement cells in these smears can be depended upon to rule out the possibility of incomplete abortion in cases of excessive vaginal bleeding.

#### VAGINAL SMEAR CHANGES IN PREGNANCY AND AFTER PARTURITION AS COMPARED TO THOSE NOTED IN CASES OF INCOMPLETE ABORTION

Pregnancy is characterized by extensive growth and secretory phenomena in the corpus luteum and uterus. These activities correspond to those taking place in the premenstrual phase of a normal menstrual cycle but are much more pronounced.

Stieve has described the morphologic changes taking place in the human vaginal epithelium during pregnancy. He says, the termination of pregnancy results in a very pronounced destructive phenomenon and that with the onset of parturition the vaginal epithelium undergoes extensive denudation. We have found both gross and microscopic evidence of the same activity. The majority of cells found in vaginal smears taken post-partum substantiate this condition. They are apparently derived from the deeper outer basal zone, and usually show a compact round or oval form or may be navicular in shape. The nucleus is large, slightly oval and often displaced to one side, or may show vacuoles around it. We looked for these cells in all smears taken from patients suspected of having an incomplete abortion that came under our care on the Gynecological Service of Firmin DesLoge Hospital for a period of two years.

#### PLAN OF PROCEDURE

Daily vaginal smears were taken from every patient entering the hospital with a tentative diagnosis of incomplete abortion and also from those in whom this possibility could not be definitely ruled out. This was continued until the patient was curetted. Twenty-four hours after operation daily "smearing" was resumed, using strict aseptic precautions and continued until the patient left the hospital. No difficulties or complications were encountered in this practice.

Smears were taken at regular intervals from pregnancy cases in various stages of development, usually weekly or bimonthly, and were continued on individual cases as long as it was possible to contact them in the prenatal clinic. These periods varied from one to seven months. Contacts were established in some instances as early as the tenth week and in others from the sixteenth to the thirty-third week. Whenever possible, contacts started late in pregnancy were maintained until the patient entered the hospital for delivery, and then were continued throughout the first two weeks post partum.

A large series of vaginal smears were taken at random from prenatal cases at practically all periods of gestation. The number of days since the beginning of pregnancy was noted on each slide. The same was done on post-partum cases during the first two weeks of the puerperium, and in four cases this was again resumed after the sixth week and continued at weekly intervals for three to seven weeks more.

A series of vaginal smear specimens composed of daily smears taken from normal individuals for one, two, and three consecutive menstrual cycles were



As previously stated they are so consistently present in smears from cases of incomplete abortion that eventually we may be able to establish them as a definite, easily recognized sign of this condition which can be brought out by a relatively simple staining process.

Red blood cells, as might be expected, are abundant.

White blood cells are variable. In some instances they are surprisingly scarce but as a rule are present in considerable numbers and, in the presence of secondary infection, they dominate the picture. The presence of large numbers of polymorphonuclears, displaying evidence of high phagocytic activity, suggests the presence of secondary infection before other clinical symptoms and signs develop.

Mononuclears having a peculiar type of degeneration were observed in almost every smear studied in the incomplete abortion series. They are larger than normal and their nuclei is small, shrunken, fragmented, or absent. The cytoplasm is almost completely vacuolized while the cellular outline is distinct, discrete, and intact. At first this gave the impression of intercellular vacuole formation which had resulted from drying or some other type of artefact. However, their consistent presence and regularity in appearance warrant their consideration as a factor in these smears. They were carefully looked for in other types of

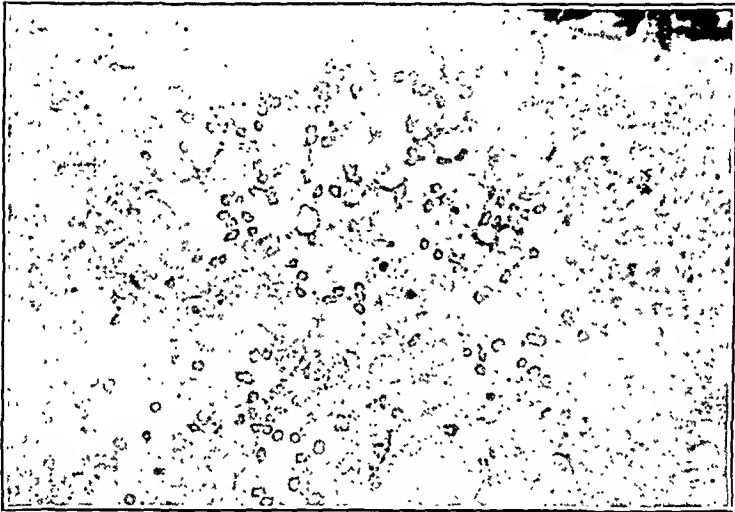


Fig. 4.—Mononuclear degeneration and vacuolization in case of incomplete abortion.

smears but were observed only once elsewhere, in a post-partum smear taken on the fifteenth day, from a patient making an uneventful recovery from a low cervical type of cesarean section. These cells were present in all incomplete abortion smears regardless of the type of staining technique used (Fig. 4).

In uncomplicated cases of incomplete abortion, mucus is present in relatively small amounts, and in some instances it is definitely absent. In the presence of secondary infection, it increases in proportion to the degree of activity caused by the infection and seems to be in proportion to the increase in number of leucocytes. In one case in our series, mucus was so abundant and so thick that it almost completely obscured the cellular aspect of the picture.

The amount of general debris corresponds sufficiently in all smears with the variations in amount of mucus to suggest that it be considered in conjunction with this fact.

#### TECHNIQUE FOR THE PREPARATION OF THE VAGINAL SMEAR

Our attempts with the use of the glass pipette suggested by Papanicolaou were unsatisfactory. After trying various procedures we were satisfied with results obtained by taking a swab from the vaginal wall with an ordinary wooden applicator, having a moderately-sized piece of cotton wrapped around one end,

large nucleus that stains a darker shade of blue. They are well defined, discrete, round, oval or slightly irregular in shape. They show no indication of wrinkling or folding because they are too small. They correspond in general appearance to the outer basal cells but are smaller and more consistent in shape. We believe these two types of cells are indicative of incomplete abortion.

It seems reasonable that their presence may be accounted for by the fact that in the majority of instances, patients with an incomplete abortion are inclined to permit the condition to persist for relatively long periods of time before seeking medical advice and help. These women may be inclined to assume that their

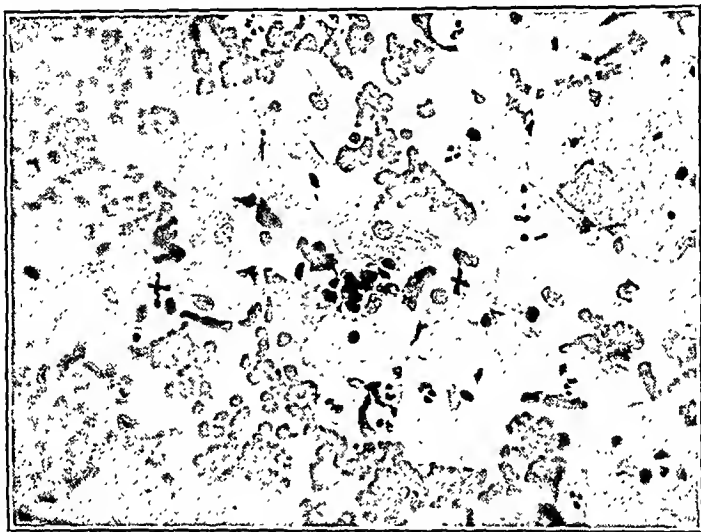


Fig. 2.—Superficial cells in case of incomplete abortion.

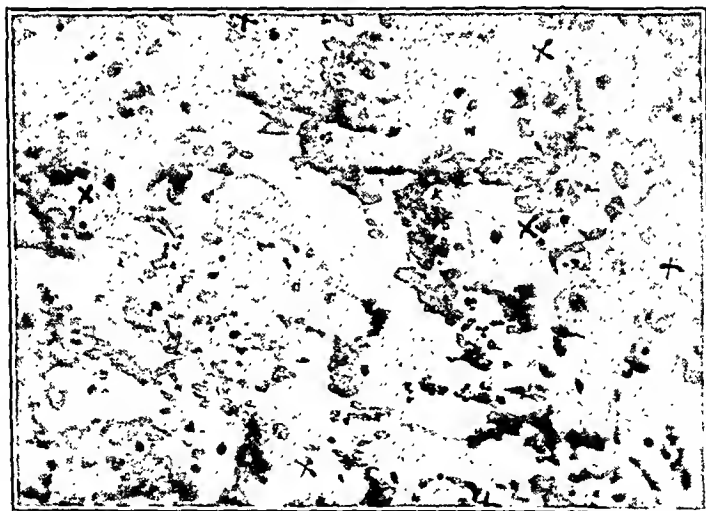


Fig. 3.—Inner and outer basal cells in case of incomplete abortion.

persistent vaginal bleeding is due to overwork, nervousness, domestic difficulties, fear, etc., and "will probably stop on its own accord within a few days." They are not seriously incapacitated and so may not be greatly alarmed about this condition until it has persisted for several weeks or months. Hence, we feel that the desquamative processes going on in the vaginal epithelium become more extensive and eventually involve these deeper layers of the vaginal epithelium.

consists of a small bottle of Ehrlich's hematoxylin stain and a small bottle of 0.1 per cent eosin in 60 per cent alcohol.

The smear is taken with a small wooden applicator having a pledget of cotton wrapped around one end. This may be used dry or may be dampened with tap water. When used wet all excess water should be expressed. The smear is taken by stroking back and forth over the surface of the lateral wall in the middle third of the vagina, then the swab is *rolled* over one-half of a clean glass slide until a good spread is obtained. It is then fixed in equal parts of ether and alcohol for half an hour or a week without causing any appreciable damage to the smear. Satisfactory smears may be made without fixing if stained immediately, but we prefer to fix them first. It is then placed in a recently filtered solution of hematoxylin, prepared as outlined, for one minute, washed in running water and placed in a 0.1 per cent eosin in 60 per cent alcohol for twenty seconds then again washed in water. If hot or warm water is used the slide dries faster. After drying it is examined under the microscope with a low power lens. Mounting with a cover slip is advisable only when the slide is to be preserved.

#### SUMMARY

1. A short résumé of the history of the development of the vaginal smear is given to show that, while it is still a relatively new procedure, it has been studied sufficiently to be recognized as a definite scientific entity, with rather well-defined clinical potentialities.

2. The histomorphology of the vaginal epithelium has been investigated in many different ways. Although all investigators are not in complete agreement as to details, the general histologic facts have been recognized and accepted. It is these generally accepted facts that have been outlined and described in this paper and used as a basis for this work.

3. We have followed the technique described by Papanicolaou in the preparation of the vaginal smears. We have modified this technique somewhat in ways which seem to us to improve the detail and clarity of the smear. These modifications have rendered the vaginal smear more applicable for the type of work we have undertaken. A further modification has been developed to simplify the staining procedure in an endeavor to make this procedure available for office and clinic use.

4. Vaginal smear changes during pregnancy and after parturition have been carefully studied, for comparison with the changes noted in cases of incomplete abortion.

5. An endeavor has been made to recognize and identify changes in the vaginal smear that might be characteristic of incomplete abortion. Certain features of the smear that seem to qualify have been described in detail. It is suggested that these might be considered as definite signs of incomplete abortion. This paper is intended as a preliminary report and is not an endeavor to establish these findings as facts at this time.

6. Our plan of procedure has been outlined, the types of controls used have been explained and a résumé of our findings, has formed the basis for this paper.

applying it to either lateral wall in the middle third of the vagina, and turning it completely around twice. The material thus obtained was immediately transferred to a clean glass slide by *rolling* the swab back and forth twice in each direction, placing the slide in a half pint mason fruit jar, containing equal parts of ether and 95 per cent alcohol and allowing it to remain in this solution for at least an hour. Sometimes it remained there a week before being stained.

Our best results with staining were obtained by modifying the technique of Papanicolaou in the following manner.

Each slide was rinsed well in 70 per cent and 50 per cent alcohol, respectively, washed smooth in tap water and placed in Ehrlich's hematoxylin for two minutes, then transferred to a jar of running tap water and washed until the water in the jar was clear. Next it was placed in 0.5 per cent eosin in 30 per cent alcohol for one minute and again rinsed in water until the slide was "smooth," then placed in a solution of 0.5 per cent water-blue for five to twelve seconds, depending upon the thickness of the spread and the age of the stain, washed again in tap water and carried through 95 per cent alcohol, absolute alcohol and xylol until all "streaks" disappeared. This was accomplished by repeated rinsing in each solution. The slide was then mounted in Gum de Mar. Mounting, however, is unnecessary unless the slides are to be preserved. The exposed slide may be studied very satisfactorily under low power without "cover-slipping."

This procedure seemed to bring out color contrasts, cellular outline and detail more satisfactorily and more consistently than any other procedure tried.

In an endeavor to develop a more simple staining technique which would be applicable for use in the clinic or office and at the same time fulfill the requirements for a satisfactory vaginal smear, we were encouraged by results obtained after modifying the technique used by Dr. A. E. Doisy in his studies of vaginal smear changes in mice and rats.

It was obvious that hematoxylin and eosin would be necessary in any type of procedure since nuclear and cytoplasmic characteristics were being considered.

Dr. Doisy uses an aqueous solution of hematoxylin prepared by dissolving 1 Gm. of the crystals in 300 c.c. of distilled water and heating. Then 100 c.c. of a saturated solution of ammonium alum is added and the mixture allowed to stand for ten days. It is then filtered each time before using. Slides are placed in this solution for sixty to seventy-five seconds, removed, and washed in warm running tap water, then placed in a 0.1 per cent solution of eosin in 60 per cent alcohol for five to ten seconds and washed again in warm tap water, allowed to dry, and examined under the microscope.

After trying various time combinations and stains of different ages, we found that satisfactory results could be obtained by allowing slides to remain in a filtered solution of hematoxylin, of any age, for one minute and in 0.1 per cent eosin solution, in 60 per cent alcohol not more than one month old, for twenty seconds. The time was increased to thirty seconds when older eosin solutions were used. We found that solutions not used too frequently could be used for several months, since frequent use obviously causes dilution. A realization of the possibility of such staining solutions remaining in an office or clinic laboratory for long periods of time is what prompted us to consider this phase of our staining problem.

Although this staining technique leaves much to be desired in studying some types of vaginal smear problems, our results with this method lead us to believe that the various factors which seem to characterize the smear of incomplete abortion can be satisfactorily identified when it is used.

#### ADAPTABILITY OF THIS PROCEDURE AND TECHNIQUE TO OFFICE AND CLINIC USE

The various features which tend to characterize the vaginal smear of incomplete abortion, as described above, can be brought out by the simple hematoxylin-eosin staining technique used by Doisy, with our modification. The equipment necessary to institute this procedure

We have used the smear staining technique of Papanicolaou and the technique that Drs. Fletcher and Doisy developed. We have not found these definite changes that he has found. We have occasionally noted these vacuolated pavement cells, but not as regularly as Dr. Fletcher has reported.

I would like to ask him upon how many cases this has been done and what is his percentage of positives as compared with other positive cases determined by the curette. Also, does he find the same things in tubal abortion as in regular abortion?

DR. PHILIP F. SCHNEIDER, EVANSTON, ILL.—We have not used this technique on the pregnant patient except in the early stages, but the data that Dr. Fletcher has presented certainly indicate that we can gain a great deal of knowledge from them.

The kodachrome slides I present represent smears which demonstrate the various pictures encountered, not only in menopausal patients but in other gynecologic conditions and even in disturbances during pregnancy, particularly nausea and vomiting. The first one is a smear taken before the patient received any therapy and shows an almost total absence of the normal cornified epithelial cells, with the presence of a large number of leucocytes and the basal cells that Dr. Fletcher mentioned.

The second specimen was taken after estrogenic therapy. The leucocytes and basal cells have disappeared, and the cornified epithelium appears. This fact is demonstrated by the increased affinity of the cell for eosin stain and indicates as shown by Papanicolaou that cornification is due to increased estrogenic action.

The third specimen shows that with an excessive amount of therapy cornification increases and intense eosin stain results with curling of the cells. In this particular patient excessive therapy was manifested not only by the smear but by a return of the same symptoms that she had prior to therapy when a deficiency existed.

I emphasize the above findings particularly since they seem to show that when basal cells are encountered in the vaginal smear they indicate estrin rather than progesterone deficiency, and that the presence of basal cells in those cases of abortion presented by Dr. Fletcher may have been due to the fact that estrin rather than progesterone deficiency has been the etiologic factor.

From our work we believe that we may learn more from the smears than from quantitative determinations of estrin, pregnanediol and gonadotropic hormone, and that the vaginal smear method may give us a more accurate though relative method of checking estrogenic activity.

In regard to the modification of technique Dr. Fletcher has suggested, we believe that rigid adherence to the technique outlined by Papanicolaou is indicated in each instance until its limitations are exhausted before attempts at simplification or modification are attempted or introduced.

7. The adaptability of this procedure for office and clinic use has been shown by an explanation of the surprisingly simple staining procedure that has been developed and found to fulfill the requirements necessary to bring out changes in the vaginal smear that seem to be characteristic of incomplete abortion.

### CONCLUSIONS

1. The vaginal smear, as a potential diagnostic feature, is available for clinical use.

2. The vaginal epithelium undergoes definite cyclic changes that correspond to changes taking place in other parts of the female generative tract. These changes may be recognized by a study of the proliferative and desquamative processes that reflect themselves in the changes taking place in the cells of the vaginal epithelium.

3. These changes can be studied by the vaginal smear method. These smears may be satisfactorily prepared by using various types of staining combinations according to definitely established staining procedures.

4. A simplified procedure for the staining of vaginal smears in the clinic or office has been developed and outlined.

5. Vaginal smear changes that seem to characterize the condition of incomplete abortion have been pointed out and described.

6. It is suggested that these characteristics may eventually be established as definite diagnostic signs of incomplete abortion.

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MISSOURI THEATER BUILDING

### DISCUSSION

DR. L. M. RIORDAN, St. Louis, Mo.—The "smear technicians" are able definitely to determine cyclic changes in the endometrium or vaginal mucosa while those who do deep biopsies are not. It was a very logical thing for Dr. Fletcher to try to adapt these procedures to the diagnosis of incomplete abortion.

In our series there were 13 cases: Each patient had aborted twice or more and did not have a living baby. The exception was one patient who had a mature living baby followed by two spontaneous abortions. Of the 13 patients treated, 11 went to term and had spontaneous deliveries. One patient aborted at four months' and the other at six months' duration of pregnancy.

The following 6 case histories are representative of the whole group:

CASE 1.—The patient, a 31-year-old para 0, gravida iii, stated that her first pregnancy ended in abortion at ten weeks. The second and third pregnancies ended in abortion at eight and ten weeks, respectively. Her fourth pregnancy was an ectopic with operation on Sept. 19, 1933. This was her first appearance at our clinic. She had changed physicians several times and had received various types of treatment, but had received no endocrine treatment excepting thyroid. A complete physical examination was done by us and nothing remarkable was found. Her laboratory findings were within normal limits and the basal metabolic rate was +8.

The patient was seen on April 24, 1934, having had her last menstrual period on March 8, 1934, and having missed her expected period by two weeks. She was advised to take complete bed rest on May 11, 1934, when she commenced to stain, and it was thought that she was going to abort. Dr. Frederick L. Hisaw was consulted and furnished us corpus luteum (Hisaw's corporin) extracted by him from pigs' ovaries and properly standardized as to the rabbit unit dosage. This patient was given five rabbit units weekly, covering a period of twenty-eight weeks. This dose was unnecessarily large, as we know at present. The preparation then in use gave marked skin reactions, was in its experimental stage as to vehicle and clearing of its foreign protein; however, no abscess formation was observed. This patient was asked to cut her work and activities to a minimum. The patient's estimated date was Dec. 15, 1934, and she was delivered Dec. 13, 1934, of a normal, living male infant, weighing 3,508 Gm. The patient has had two spontaneous deliveries at term with normal living babies since the first term delivery and has received no endocrine treatment.

CASE 2.—A thirty-eight-year-old para 0, gravida iii, whose first pregnancy ended in abortion at three months in 1933. The second pregnancy a year later in 1934 ended in abortion at three and one-half months, and the third pregnancy a year later in 1935 ended in abortion at five months. During this period of three years, she had changed obstetricians three times. The patient was subjected during these periods of pregnancy to complete bed rest, tonics, thyroid, iodine, wheat germ oil, diet regulation, wearing of a pessary, and vitamin therapy. This patient was seen by us for the first time on Sept. 16, 1937. A complete physical examination was done and revealed little information, excepting a third degree retroversion of the uterus. The laboratory reports, which included a complete blood count, urinalysis, and blood chemistry, were within normal limits. Her Wassermann reaction was negative. The basal metabolism was +4. An endometrial biopsy was recommended and performed on the twenty-first day of the menstrual cycle and showed a poorly developed secretory endometrium. Her husband was given a thorough physical examination, including a prostatic examination and basal metabolism, and was found to be normal. No therapy was advised.

Dependent upon the endometrial findings, the patient was advised to take anterior pituitary gland injections. However, she failed to appear for treatment and returned three months later having missed her last menstrual period by a week. She was placed upon three rabbit units of corpus luteum extract weekly for twenty-six weeks. She was advised to reduce her activities to a minimum but was not placed at complete bed rest. Her last menstrual period was Dec. 4, 1938. Her estimated date was Sept. 23, 1938. The baby, a normal male, weighed 3,680 Gm.

CASE 3.—A twenty-two-year-old para 0, gravida iii, whose first pregnancy was an abortion at four months. The second pregnancy was an abortion at six weeks, and

# THE MANAGEMENT AND TREATMENT OF HABITUAL ABORTION\*

WITH ESPECIAL EMPHASIS ON THE USE OF PROGESTERONE

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HABITUAL abortion is still one of the most discouraging conditions to deal with in the field of medicine.

Spontaneous abortion presents a diversity of causes, such as: abnormalities, displacements, and inflammations of the genital tract; infectious diseases; germ plasm defects; tumors of the genital organs; dietary deficiencies; vitamin deficiencies; many alleged causes indicating serious investigation; and, last, the endocrine system in which the thyroid, ovaries, and pituitary gland are so important.

Important chemical investigations in endocrinology as related to the thyroid gland, ovaries, and pituitary gland, coupled with recent experimental data upon function, have been responsible for such advances in therapy as the use of progesterone and progestin-like extracts in the treatment of habitual abortion.

It has been very well established in the human being that the corpus luteum remains active until about the fourth month of pregnancy, and then begins to degenerate slowly until about the seventh month, when there remains little evidence of its presence or activity.

It has been shown experimentally in animals that the corpus luteum substance is necessary for the maintenance of normal pregnancy. There is every reason to believe that this stabilizing factor is present in the human being until the placenta is a controlling factor.

Experimental studies by Falls and his collaborators show very clearly in the human being that the estrogenic substance increases uterine irritability and muscle contraction, and the corpus luteum substance is the antagonistic factor. It was also shown that progesterone nullifies posterior pituitary response. These findings are important in relation to habitual spontaneous abortion and its treatment.

J. C. Hirst, of Philadelphia, in 1918 was probably one of the first to use corpus luteum extract in the treatment of habitual abortion. Falls, Krohn, and Lackner in 1935, Elden in 1938, and Kane in 1936 have reported favorably on the use of progesterone and progestin-like extracts in the treatment of habitual abortion. Carl Huber, of Indianapolis, in an unpublished series of cases of habitual abortion, has had favorable results with progesterone in the treatment of his patients.

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The participation of Dr. Frederick L. Hisaw and Dr. Roland K. Meyer in this investigation is gratefully acknowledged.



arations were on the market. We still feel that one to two rabbit units weekly is a safe dose so far as therapeutic effect is concerned.

Kane and others have used comparatively small doses of progesterone; however, the dosage necessary to prevent abortion is still empirical.

The Wassermann reactions in all cases were negative. In this series the authors were anxious to use only progesterone or the progestin-like extracts in order to find their single therapeutic value. Kane and others combine the progesterone with thyroid and sodium iodide to stimulate glandular activity in general; there can be no contraindication to such treatment when carefully controlled. Others combine the above with the use of wheat germ oil, which has proved effective in the treatment of habitual abortion as a single treatment.

J. Young feels that in habitual abortion there is a disturbance occurring in the metabolism of pregnancy in which a deficiency of vitamin E is involved.

### CONCLUSIONS

This selected series presents little doubt as to the value of progesterone and corpus luteum extracts in the treatment of habitual spontaneous abortion. This treatment should not substitute for thyroid deficiencies and other obvious factors which may be responsible for the repeated spontaneous abortions. Let us be cautious in the present day *furor* of endocrine therapy to make certain that endocrine treatment is indicated and not a *misdirected substitute*!

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4133 MANITOU WAY

### DISCUSSION

DR. FREDERICK H. FALLS, CHICAGO, ILL.—If we give two ampoules of one rabbit unit of progesterone weekly after a patient with a history of habitual abortion has missed her first period, the cost to the patient for progesterone alone will amount to about one hundred and fifty dollars if she is carried on this dosage until the thirty-fourth week.

Dr. Campbell's figures show a percentage of 85 per cent successes. This corresponds to our combined series of 38 cases in which we got living babies that survived in 81 per cent. Our cases included patients who had a history of habitual abortion, and in many cases had symptoms of threatened abortion at the time treatment was begun.

We have tested a number of commercial preparations in the laboratory, using the intrauterine bag method in the seventh day of the puerperium. We find great differences in the amount of inhibition of uterine contractions produced by the injection of different products.

More recently we have been using the old corpus luteum extract proposed by Hirst in 1918, in the treatment of both abortion and hyperemesis gravidarum. We were told that progesterone was only soluble in oil and that therefore none

the third pregnancy was an abortion at two months. All of her pregnancies were accompanied by severe nausea and vomiting, and the abortions were preceded by severe menstruallike cramps. This patient, like others in the series, had seen more than one physician and her treatment was diversified. The only endocrine treatment was thyroid administration. Her last period was April 18, 1937, and she was seen by us about five weeks subsequently. It was necessary because of nausea and vomiting to admit her to the hospital and give her treatment for vomiting of pregnancy. She was dehydrated, with acetone in the urine and on the breath.

She was started on a weekly dose of two rabbit units of progesterone while in the hospital, and the treatment was continued for twenty-eight weeks. The estimated date of confinement of this patient was Jan. 25, 1938, and she delivered Jan. 20, 1938, a normal living girl weighing 3,350 Gm.

CASE 4.—The first pregnancy of a thirty-year-old para 0, gravida ii, ended in a two months' abortion on Nov. 1, 1933, and the second pregnancy of ten weeks' duration ended in abortion on Oct. 31, 1934. During these two pregnancies the patient had experienced almost daily staining and menstruallike pains. On April 15, 1935, she had her last period and was pregnant for the third time. She was seen ten days after her May period should have appeared and was placed on three rabbit units of progesterone weekly for twenty-six weeks. She stained and passed clots throughout the first four months. Bearing down pains accompanied the entire pregnancy. This patient was diagnosed by the obstetric service as the hebephreniac type of dementia precox, and this diagnosis was not confirmed by the psychiatric service. The patient became troublesome and finally dissatisfied with our services, and transferred to another clinic where she was delivered at term of a normal living baby.

CASE 5.—A twenty-five-year-old para 0, gravida ii. This patient gave a history of two abortions at six weeks in 1933 and two months in 1934. Throughout both of these pregnancies she had almost daily vaginal staining accompanied by menstruallike cramps. On Jan. 8, 1935, she had her last menstrual period and was pregnant for the third time. The patient was placed upon two rabbit units of progesterone weekly for twenty-eight weeks. She delivered at term a normal living baby, weighing 3,600 Gm.

CASE 6.—A twenty-eight-year-old para i, gravida iv, delivered at term in 1935 of a living child. The patient aborted once in 1936 and twice in 1937. On Oct. 15, 1938, she had her last normal menstrual period and missed her November period. She was seen after missing her November period by a week and was placed upon two rabbit units of progesterone weekly for twenty-six weeks, and delivered a normal male infant, weighing 4,086 Gm.

#### DISCUSSION

Each patient in this series was very carefully checked by physical examination to exclude every possible causative factor as related to habitual abortion. Many of these factors have already been mentioned. Laboratory data were obtained, including a Wassermann test in all instances; in addition, patients admitted for study with histories of repeated spontaneous abortions have had basal metabolic rates taken, and an endometrial biopsy to study the secretory phase of the endometrium. Pregnanediol studies were useful, as well as studies of vaginal smears by the method of Papanicolaou. The authors feel that in certain instances a thorough examination of the husband should be made, including basal metabolic studies in some individuals. The babies were not excessive in size, presented no fetal abnormalities, and 11 were living. The progesterone dosage used in the several cases varied considerably and was much higher in the earlier years of treatment long before the commercial prep-

ment was instituted. These results were accomplished in the presence of a minimum dosage of the far more expensive progestin, and minimum sedation. In my opinion, patients with histories of habitual abortion should receive dehydrated young grasses before conception and throughout pregnancy.

DR. PHILIP F. SCHNEIDER, EVANSTON, ILL.—I would like to ask Dr. Campbell as to the number of cases in which progesterone has been unsuccessful in continuing pregnancy, following habitual abortion.

I should like to refer to two patients, showing weekly pregnanediol determinations, each of whom threatened to abort early during pregnancy, both sterility patients, one of five and the other seven years. From the eighth week, weekly pregnanediol determinations were obtained. At about the eighth or ninth week both patients threatened to abort as manifested by cramping and bleeding. With an increase in the amount of estrin in Case 1, the threat to abort subsided and the patient continued normally throughout pregnancy. The estrin was discontinued about the fourth month. The same result was obtained when the amount of progesterone was increased in Case 2. I think this observation is of particular interest, because it shows that quantitative values obtained apparently do not mean a great deal. In this instance two patients, one with very high pregnanediol values and the other with very low pregnanediol values carried through pregnancy uneventfully. This would seem to corroborate the suggestion of Novak that balance between the estrin and progesterone rather than the quantitative amounts of one or the other is the important factor.

DR. CAMPBELL (closing).—In answer to Dr. Schneider, we failed in two patients with histories of habitual abortion and, as far as treating threatened abortion is concerned, we have had little or no success.

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## SPONTANEOUS PNEUMOTHORAX OF THE NEWBORN INFANT\*

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**S**PONTANEOUS pneumothorax of the newborn infant should not be classified as a medical curiosity. It is a clinical entity which probably occurs frequently and is usually overlooked. No papers on the subject are to be found in obstetric literature, although references may be found in the pediatric and roentgenologic literature. This condition, certainly in its acute form, should command the attention of every obstetrician. The occurrence at Michael Reese Hospital of two instances of spontaneous pneumothorax in the newborn infant within one month is considered of sufficient interest to warrant this presentation.

CASE 1.—A white male, first child of a normal, 26-year-old mother, was born spontaneously after sixteen hours of labor. The second stage was of sixteen minutes' duration. The baby was cyanotic from birth but gave an occasional labored gasp. A swelling was visible over the upper portion of the sternum. Mucus was removed from the baby's throat and external stimulation was employed, but without avail. A tracheal catheter was therefore passed, and for thirty minutes tracheal insufflation was carried out by the House Staff. During this period the baby gasped

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of the watery preparations could contain progesterone. Testing the corpus luteum extract, however, soon proved that 1 c.c. of the watery solution contained approximately one-tenth of a rabbit unit of progestin.

A word may not be amiss at this time regarding the use of morphine in the treatment of these patients. It will be seen from the tracings that if morphine does any good at all it certainly is not due to its inhibitory action on uterine contractions.

Finally, I should like to call attention to the similarity between spontaneous abortion and ablatio placentae. It seems to me quite probable that the same factors are at work in the two conditions; namely, increased uterine irritability and intrauterine hemorrhage. If this is so, the same management should apply to both conditions. This we find to be the case if we limit the treatment to those patients showing partial separations and apparent hemorrhage. We have found that progesterone will control the hemorrhage and stop further separation of the placenta and allow the pregnancy to go to term. In these patients in whom the fetus is on the borderline of viability at the time the first hemorrhage occurs, this is of the greatest importance. We have been able to cut the fetal mortality to 15.3 per cent in a series of 19 cases.

DR. CARL P. HUBER, INDIANAPOLIS, IND.—It is extremely important that the group of patients treated with corpus luteum hormone be limited to those who have had at least two previous abortions, and also that they be a group of patients in whom no other demonstrable cause for abortion is found. Prophylactic treatment of patients who have had one abortion in the first pregnancy is hardly justified.

During the past three years at the Chicago Lying-in Hospital and at the Indiana University Medical Center, I have collected a group of 15 patients who gave histories of repeated spontaneous abortions. Eight of them had two previous abortions. Seven had from three to seven previous abortions. In all but one of these cases, the pregnancy was carried to term. The amount of corpus luteum hormone which we used averaged one rabbit unit each week with two injections of one rabbit unit each being given during the week the patient would menstruate if she were not pregnant. The treatment was continued until a few weeks before term.

We have used both biologic and synthetic corpus luteum preparations and have been able to demonstrate no difference in their effects.

In the management of patients with threatened abortion, the results have not been nearly as satisfactory. The percentage of patients treated actively with corpus luteum therapy who failed to abort is small. I suspect that the reason lies in the fact that in many instances a patient who shows evidence of threatening abortion is aborting for some other reason than failure of corpus luteum hormone production.

DR. J. M. SINGLETON, KANSAS CITY, Mo.—In July, 1938, I was confronted with two cases of threatening abortion where progestin, lutein, wheat germ oil, and sedation were failing. Vitamin K in its control on bleeding came to mind and this was administered in the form of dehydrated young grasses, with the hope that decidual hemorrhage would thus be inhibited. The results were almost immediately gratifying. Later investigation into the properties of dehydrated young grass revealed that it contained, in addition to vitamin K, factors which might play an even more important role in providing a continuously healthy nidation area. These are principally the gonadotropic factor described by Friedman, the grass juice factor, the reproductive and growth factors of Norris shown to be essential for high percentage in matching of eggs and vitamin E.

Of the 35 patients treated subsequently in this manner, 15 had a history of one or more previous spontaneous abortions and 3 should be placed in the habitual abortion class. Of the 15 cases, 11 patients continued with pregnancy. Of the three classed as habitual abortions, two continued with pregnancy. The one who aborted probably had a complete separation of the ovum before treat-

Roentgenogram of the chest taken the following morning revealed a small amount of air still present in the right pleural cavity, subcutaneous emphysema, mediastinal emphysema and pneumoperitoneum.

CASE 2.—A white, female baby, weighing 3,170 Gm., was born to a normal secundipara after four hours' labor. The duration of the second stage was fifty minutes. Delivery was spontaneous and resulted in a second degree laceration of the perineum. No abnormalities were noted at the time of birth, but on the following morning, during routine examination, the pediatrician on service observed a mild cyanosis with distant heart sounds. A roentgenogram taken shortly thereafter revealed pneumothorax on the left side with about 20 per cent collapse of the left lung and displacement of the mediastinum and heart to the right. Since the baby's condition was very good, no special treatment was instituted. A second roentgenogram taken six days later revealed complete absorption of the gas, with return of the mediastinum and the heart to normal position.

#### REVIEW OF LITERATURE

Sixty-seven instances of pneumothorax occurring during the first few months of life have been found in the world literature. This study considers only the 46 instances which occur in direct connection with birth plus the two cases herein reported. Ten days has been set as the maximum time for the recognition of pneumothorax associated with birth. This arbitrary time limit eliminates, therefore, 21 reported cases, many of which were in association with inflammatory lung processes or congenital anomalies. For a more complete recapitulation of spontaneous pneumothorax occurring in older infants, attention is called to the publication of Coccheri and Rossi.<sup>1</sup>

Analysis of the 48 instances, those definitely associated with birth, makes it apparent that there exist two distinct forms of pneumothorax. The first is illustrated by Case 1 herein reported. The symptoms date from birth or shortly thereafter. The baby is deeply cyanosed, dyspnea is marked and stridor may be present; the baby is unable to cry. Percussion usually reveals unilateral hyperresonance of the chest with displacement of the mediastinum and heart dullness. Roentgen examination will reveal complete or nearly complete collapse of one lung, with or without involvement of the other lung. Fourteen patients fell into this group, which, because of the sudden onset and critical condition, might well be designated *pneumothorax abrupta*. Six deaths occurred in this group, a mortality of 42.85 per cent. Furthermore, it is probable that at least two others would have succumbed had it not been for prompt aspiration of the chest. Aspiration was employed four times<sup>2-4</sup> in these 14 cases without a death.

Thirty-four patients presented a clinical picture similar to that of Case 2 which might be designated *pneumothorax lenta*. The symptoms are mild and include a gradual onset of cyanosis, perhaps noticed only when the baby cries, rapid respiration, and physical findings which may or may not reveal hyperresonance and displaced cardiac dullness. Roentgen examination reveals partial but occasionally even complete pneumothorax. Recognition of this type of pneumothorax was frequently late and often an accidental discovery. It must be emphasized, however, that the main difference between the two types lies in the severity of symptoms and rapidity of onset. In that group classified as *pneumothorax lenta*, only two babies died, both of cerebral hemorrhage,<sup>5, 47</sup> while aspiration was employed twice.<sup>6, 7</sup> Special treatment, if any, consisted of O<sub>2</sub> or CO<sub>2</sub> - O<sub>2</sub> inhalation, and respiratory stimulants.

In every surviving baby in the entire group, the pneumothorax disappeared within two to sixty days with the exception of the baby reported by Tideström.<sup>6</sup> Apparently this patient had a pulmonary fistula and probably should not be included in this series; it might well have been a congenital anomaly, as a thoracoplasty was performed subsequently.

Clinically there are only a few conditions that must be distinguished from pneumothorax in the newborn infant. Most common is simple blockage of the respiratory tract with aspirated material. Once the material is removed, spon-

with difficulty and remained deeply cyanosed. Upon examining the baby at this time, it was apparent that the swelling over the sternum was caused by subcutaneous emphysema. The tracheal catheter was passed again and insufflation resumed. It was observed that the air entered the lungs with unusual difficulty. On percussion of the chest, the right side was hyperresonant and the diagnosis of right pneumothorax was made. A needle was introduced into the right pleural cavity, and 100 c.c. of air were aspirated. Immediately and almost dramatically the baby became pink, normal respiration was established, and the baby cried lustily. For the next twelve hours the baby was kept in an oxygen incubator. Convalescence was uneventful. There was no recurrence of the pneumothorax.



Fig. 1.—Case 1. Partial right-sided pneumothorax and left pneumoperitoneum.



Fig. 2.—Case 2. Partial left-sided pneumothorax.

common etiology, dependent upon increased intrapulmonic pressure and inability of the tissue to withstand that pressure. Of course, it is conceivable that direct lung injury and perforation by a fractured rib or clavicle might result in pneumothorax, but there is no definite proof of such a condition occurring.

To date, almost every author,<sup>41</sup> concerned with the clinical aspect of so-called spontaneous pneumothorax, has expressed the view that the pneumothorax results from the rupture of a subpleural bleb, the latter associated with alveolar rupture. Even Escudero and Adams<sup>42</sup> in their experimental work on massive atelectasis in dogs state that the observed pneumothorax results from rupture of a bleb on the hyperinflated side. Autopsy findings of dilated and torn air sacs,<sup>3, 15</sup> and in one instance of a true pleural tear,<sup>16</sup> would bear this out. However, autopsy may not reveal evidence of pulmonary injury.<sup>5, 47</sup> Likewise, with an actual rupture it is hard to conceive how a single aspiration will permit the lung to reinflate and not leak again; yet in several instances,<sup>2, 4, 7</sup> including the first case reported herein, a single aspiration of the pleural cavity was followed by complete cure. The frequent occurrence of bilateral pneumothorax<sup>8-11</sup> also makes this theory difficult to accept, because it implies rupture of blebs in each pleural cavity. Finally, the frequency of partial pneumothorax would imply either a low pressure leak, or one that rapidly seals itself.

As early as 1733 Stephen Hales<sup>17</sup> demonstrated that hyperinflation would cause air to escape from the pleural surface of the lungs without gross evidence of either bleb or rupture. In 1883 Ewald and Kobert,<sup>18</sup> repeating this work with excised lungs inflated in water, showed that the minimum pressure of inflation required to produce leakage in a given specimen remains the same on repeated tests, and that neither blebs nor tears were demonstrable. If rupture had occurred on these first tests, it would be reasonable to expect air to escape at lower pressures on subsequent trials. On this basis Kha T'i Lim<sup>19</sup> quoting Van Allen suggests that the pathogenesis may be explained by this phenomenon: air under pressure extravasates through the pleura and into the pleural cavity without rupture of the pleura.

In repeating this work with excised dog lungs inflated under saline solution, I have been unable to observe this extravasation of air from the pleural surface even at pressures of 100 mm. of mercury, a pressure far in excess of that to which the fetal lung could conceivably be subjected. Likewise, with pressures up to 100 mm. neither bleb formation nor rupture of the pleural surface has been observed.

Macklin<sup>20</sup> demonstrated that increased pulmonic tension will lead to pulmonary emphysema and extravasation of air along the perivascular sheaths into the mediastinum. Similar experiments by Joannides and Tsoulos<sup>21</sup> indicate the accuracy of this observation. I found that pressures as low as 18 to 20 mm. of mercury were sufficient to produce a bullous mediastinal emphysema in some dogs; yet there was no gross evidence of lung damage. How this air gets out of the alveolae remains to be proved. Ogawa<sup>22</sup> and others have demonstrated that pores apparently exist between alveolae in the lungs of animals, and Macklin<sup>23</sup> has described similar openings between alveolae in the human lung. Van Allen and his associates<sup>24</sup> have shown that these spaces, although normally collapsed, open under pressure, permitting communication between adjacent alveolae. It is possible that under pressure similar spaces permit air to escape into the surrounding connective tissue, following the perivascular sheaths until it reaches the very loose areolar tissue of the mediastinum.<sup>47</sup> Once mediastinal emphysema has occurred all the associated phenomena are easily understandable. Rupture of mediastinal blebs into the pleural cavities may produce right, left, or bilateral pneumothorax, and depending upon the amount of air in the mediastinum, the degree of collapse may be very slight or complete. Mediastinal emphysema may spread upward along the vessels into the cervical and axillary areolar tissue or downward through the hiatus aorticus and esophagus into the retroperitoneal tissue. From the retroperitoneal tissue a bleb could rupture into the peritoneal cavity, causing pneumoperitoneum, as in the case reported by Tunger,<sup>25</sup> or extension could occur along the iliac vessels eventually reaching the thigh through the femoral canal. Additional proof that these extensions do occur is furnished by the existence of mediastinal and subcutaneous emphysema and pneumoperitoneum in our first case as well as pneumothorax, and by the associated subcutaneous emphysema in the patient reported by Strongin.<sup>2</sup> The asymptomatic

taneous normal respiration should follow. Most difficult will be congenital lung cyst and diaphragmatic hernia. Here dyspnea, cyanosis, displacement of the mediastinum, hyperresonance, and increased resistance to tracheal insufflation will be present. Even a roentgenogram may not definitely establish the diagnosis of a lung cyst.<sup>2</sup> In addition, such conditions as atelectasis, pneumonia of the newborn, dextrocardia, and cerebral injuries must be considered.

A survey of all cases indicates that spontaneous pneumothorax occurs slightly more often in the male than in the female, and is more likely to be right sided than left. Most interesting are the 7 cases of bilateral pneumothorax in connection with which several unusual observations have been made. A. Hotz<sup>8</sup> observed an alternation from one side to the other within seven days, Riedweg<sup>9</sup> the same phenomenon in six weeks, and I. Holz<sup>10</sup> within three days. Bertin<sup>11</sup> in routine examination for enlarged thymus demonstrated normal lungs at birth but partial bilateral pneumothorax at one month. Rothman<sup>12</sup> observed bilateral pneumothorax following cesarean section.

The so-called spontaneous pneumothorax of the newborn infant may arise from several causes:

1. Congenital anomalies, such as pulmonary fistulas and abnormalities of the pulmonary vessels. Lung cysts must be distinguished from pneumothorax but such differentiation may be difficult. Pneumothorax has been confused with lung cyst,<sup>2, 13</sup> hence these cases are classed under congenital anomalies.
2. Inflammatory processes associated with small lung abscesses, either from pneumonia or septic emboli.
3. Trauma, including fractured clavicle, fractured rib, direct parenchymatous injury, and cough.
4. Mechanical obstructions such as mucus, vernix or meconium blocking the air passages, cord around the neck, struma, or enlarged thymus.
5. Artificial respiration.

In addition there is a large group in which the cause is undetermined.

TABLE I. STATISTICAL SURVEY

	PNEUMOTHORAX ABRUPTA 14	PNEUMOTHORAX LENTA 34
Average weight	3,464 Gm.	3,392 Gm.
Male	7	17
Female	4	14
Right sided	5	17
Left sided	4	13
Bilateral	3	4
Etiologic factors:		
Artificial respiration	8	2
Respiratory obstruction	1	12
Trauma	3	4
Unknown	2	16
Treated by aspiration	4	2
Died	6	2

No uncertainty exists in the pathogenesis of those cases associated with such congenital anomalies as bronchopleural fistulas.<sup>14</sup> Just how cardiac anomalies predispose to pneumothorax is not clear; perhaps the finding is incidental, but it has been observed four times in the series of 69 patients. Nor is there uncertainty in those cases associated with a pre-existing inflammatory process: an abscess forms, ruptures, and permits access of air to the pleural cavity.

The remaining cases, those associated with trauma, mechanical obstructions, artificial respiration, and that group without demonstrable cause, probably have a



TABLE II. CHIEF FEATURES OF CASES REVIEWED\*

CASE	AUTHOR AND DATE	WEIGHT	DELIVERY AND CONDITION OF BABY	AGE		SEX	SIDE AND TYPE	TREATMENT	TERMINATION	POSSIBLE ETIOLOGIC FACTORS AND REMARKS
				ONSET SYMPT.	WHEN DIAGNOSED					
<i>Pneumothorax Abrupta</i>										
1	Ruge <sup>16</sup> 1878	Premature	Breech extraction. Asphyxiated	14 hr.	1 da.	M	L C		D	Rupture of an emphysematous vesicle. 3 cm. tear found in pleura
2	Flipse <sup>3</sup> 1928	3,590 Gm.	Forceps. Moderate asphyxia	Few hr.	24 hr.	F	L C	Asp. twice O <sub>2</sub>	S	Collapse of epiglottis; artificial respiration, tracheal catheter
3	Bush <sup>4</sup> 1930	3,950 Gm.	Spontaneous	1 da.	32 hr.	M	R P	Asp.	S	Unknown
4	Emmert <sup>29</sup> 1930	?	Cesarean section	Birth	Few min.	M	L C	Con.	D	Alv. tear assumed. Artificial respiration (mouth to mouth)
5	Tollkuhn <sup>15</sup> 1932	?	Spontaneous	1 da.	24 hr.	?	R C	Con.	D	Cough and rupture of an emphysematous vesicle
6	Deissler <sup>28</sup> 1933	Term	Forceps. Cyanotic from birth	Birth	P.M.	M	B C	Con.	D	Artificial respiration and Drinker. Rupture of emphysematous vesicles
7	Deissler 1933	Premature	Difficult delivery. Asphyxiated	Birth	P.M.	?	?	Con.	D	Artificial respiration
8	Deissler 1933	Term	Difficult delivery. Asphyxiated	Birth	P.M.	?	?	Con.	D	Artificial respiration
9	Riedweg <sup>9</sup> 1934	2,720 Gm.	Spontaneous. Apnea cyanosis, and stridor	Birth	1 da.	F	A-B R P birth & L P at 1½ mo.	Con.	S	Small thyroid enlargement
10	Riedweg <sup>9</sup> 1934	1,980 Gm.	Spontaneous, asphyxiated, pale	Birth	1 da.	F	R P	Con.	S	Art. resusc. Also aspiration of liquor

\*A, Alternating pneumothorax; B, bilateral pneumothorax; C, complete pneumothorax; Con., conservative; D, died; L, left side; P, partial pneumothorax; R, right side; S, survived; P. M., post mortem.

subcutaneous emphysema that is not infrequently observed probably arises by the same process, without rupture of the mediastinal pleura. In a recent article Slot and Brown<sup>26</sup> report the occurrence of suprasternal subcutaneous emphysema in the newborn infant. The observation that little air seemed to enter the lungs, and the associated dyspnea and cyanosis, relieved only by oxygen, may indicate that they were confronted in addition with an unrecognized pneumothorax. A roentgenogram, taken after forty-eight hours and clinical recovery, failed to reveal lung pathology. It is possible that a bullous mediastinal emphysema, as observed on post-mortem examination by Schuler,<sup>47</sup> might of itself lead to both circulatory and respiratory embarrassment, with or without pneumothorax.

Another phenomenon was observed with dogs. When the pressure was quite high, 60 to 90 or more millimeters of mercury, the dog was likely to die suddenly of seeming cardiac failure. Post-mortem examination revealed, in addition to mediastinal emphysema, that the entire vascular system was filled with air bubbles and the heart

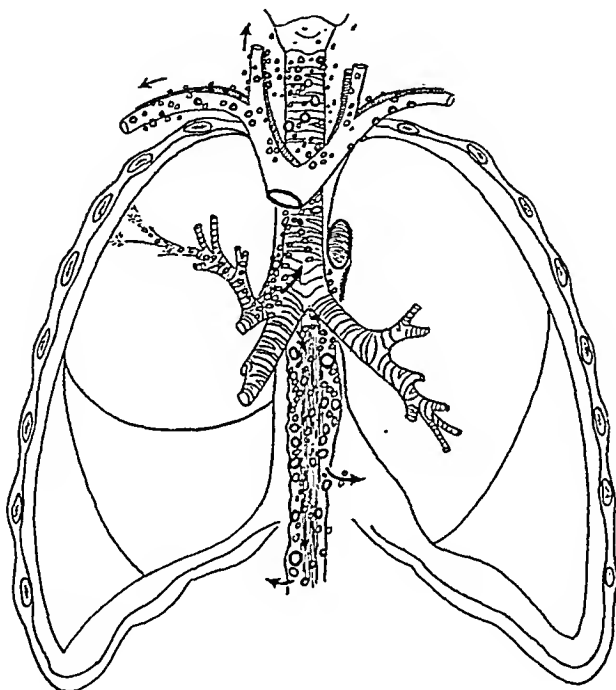


Fig. 3.—Diagram of course of extravasated air.

contained frothy blood. Air embolism seems to arise by the same process, only extravasation occurs into the capillaries. Lindblom<sup>27</sup> actually found air in the circulatory system of newborn infants who failed to respond to strenuously applied methods of artificial respiration.

Granting that these various phenomena may arise from increased intrapulmonic pressure, variations in permeability and strength of the lung tissue will greatly affect the outcome and degree of involvement. Thus it was observed that whereas 18 to 20 mm. of pressure was sufficient to cause mediastinal emphysema in some dogs, in others as much as 30 mm. were without gross effect. In a similar manner, many instances of labored respiration, including those associated with congenital malformation of the upper respiratory tract, may not lead to mediastinal emphysema or pneumothorax presumably because the baby's tissue is able to withstand the pressure to which it is subjected.

Having in mind the effects of increased intrapulmonic pressure, it becomes particularly interesting to consider further the effect of artificial respiration. For only 10 babies in the entire series of 48 is there information that some form of artificial

TABLE II—CONT'D

CASE	AUTHOR AND DATE	WEIGHT	DELIVERY AND CONDITION OF BABY	AGE		SEX	SIDE AND TYPE	TREATMENT	TERMINATION	POSSIBLE ETIOLOGIC FACTORS AND REMARKS
				ONSET SYMPT.	WHEN DIAGNOSED					
8	Hotz, A. 1934	4,820 Gm.	Spont. Child asphyxiated, Dysp. and cyanosis	1 da.	12 da.	M	L P	Con.	S	Atelectasis or cerebral hem. Alveolar tear assumed
9	Willis 1934	4,310 Gm.	Child asphyxiated	1 da.	7 wk.	M	L C	Con.	S	Cord around neck
10	Riedweg 1934	3,100 Gm.	Cyanotic	Birth	4 da.	F	L P	Con.	S	Cord around neck and shoulder
11	Riedweg 1934	2,230 Gm. on 4 d.	Spont. Cyanosis and stridor	Birth	5 da.	M	R P	Con.	S	Large thyroid, cretin habitus. Asp. liquor
12	Riedweg 1934	2,900 Gm.	Spontaneous. Cyanosis and stridor	Birth	2 da.	F	R P	Con.	S	Enlarged thyroid
13	Riedweg 1934	4,060 Gm.	Forceps. 69 hr. labor. Asphyxiated, cyanotic	Birth	2 da.	M	R P	Con.	S	Fract. clavicle, birth trauma. Subcut. hemat.
14	Riedweg 1934	3,880 Gm.	55 hr. labor. Lively baby	3-4 da.	4 da.	M	R P	Con.	S	Long labor. Thought to have congen. heart. Cyanotic at 5 wk.
15	Riedweg 1934	3,770 Gm.	Spont. Sl. cyan.	1 da.	1 da.	M	R P	Con.	S	Unknown
16	Riedweg 1934	2,800 Gm.	Spont. Cyanotic	30 min.	2 da.	M	L P	Con.	S	Unknown
17	Riedweg 1934	3,940 Gm.	Lively baby	2 da.	2 da.	F	R P	Con.	S	Sl. enlarged thyroid
18	Riedweg 1934	?	Rapid. Lively	3 da.	3 da.	F	R P	Con.	S	Unknown
19	Folke 1935	3,300 Gm.	Difficult. Asphyxia	1 wk.	3½ mo.	M	R P	Con.	S	Art. resp. by flexion
20	Heijbroek <sup>33</sup> van Ebbenhorst <sup>40</sup> 1936	4,290 Gm.	Asphyxiated	1 da.	5 da.	F	L P	Con.	S	Alveolar tear assumed. Cord around neck
21	Heijbroek <sup>33</sup> van Ebbenhorst <sup>40</sup> 1936	4,410 Gm.	No asphyxia	15 hr.	15 hr.	M	L P	Con.	S	Alveolar tear assumed. Cord around neck

11	Biedweg 1934	3,840 Gm.	Difficult, asphyx.	Birth	1 da.	M	R P	Con.	S	Art. resp., birth trauma
12	Rothman <sup>12</sup> 1937	3,660 Gm.	Ces. sect. (no indication given)	Birth	26 hr.	M	B	O <sub>2</sub> -CO <sub>2</sub>	S	Unknown
13	Strongin <sup>2</sup> 1938	4,535 Gm.	Manual rotation and difficult mid-forceps	4 hr.	4 hr.	F	L C	Asp. 100 c.c. air	S	Trauma. Erb's palsy
14	DeCosta 1939	3,110 Gm.	Spont. 17 hr. labor. Cyanosis and dyspnea	Birth	40 min.	M	R C	Asp. 100 c.c. air	S	Tracheal catheter

*Pneumothorax Lenta*

1	Scheletema <sup>30</sup> 1917	?	Spontaneous, asphyxiated	1 da.	7 wk.	M	L C	Con.	S	Unknown. Congenital anomaly assumed
2	Smith <sup>7</sup> 1919 (Reporting for Dr. Zuckerman)	(10 pounds at 7 wk.)	Spontaneous, asphyxiated	?	7 wk.	M	L C	Asp.	S	Unknown. (Died of bronchopneumonia at 3 mo.) Seen for rash on buttocks; accidental discovery
3	Tidestrom <sup>6</sup> 1924	2,975 Gm.	Spontaneous	10 da.	3 mo.	F	L C	Asp.	S	Unknown. Pneumothorax persistent, later had thoracoplasty (possibly a lung cyst or fistula)
4	Sorrentino <sup>5</sup> 1930	2,950 Gm. at 35 d.	Spont., prolonged	1-2 da.	35 da.	M	R C	Con.	D	Convulsions 3rd day; cerebral hemorrh. on P.M.
5	Lim <sup>19</sup> 1932	?	Spont., difficulty with shoulders. Cyanotic. Grunting resp. first 48 hr.	1 da.	5 da.	M	R P	Con.	S	Cord short and around neck twice. Also enlarged thymus
6	Hotz, A. <sup>8</sup> 1934	3,010 Gm.	Spontaneous	5 da.	9 da.	F	A-B P	Con.	S	Large thymus. Alt. 5 da. 1 side, 12 da. other. Alv. tear assumed
7	Hotz, A. 1934	3,300 Gm.	Spontaneous	1 da.	15 da.	M	L P	Con.	S	Unknown. Alveolar tear assumed

TABLE II—CONT'D

CASE	AUTHOR AND DATE	WEIGHT	DELIVERY AND CONDITION OF BABY	AGE		SEX	SIDE AND TYPE	TREATMENT	TERMINATION	POSSIBLE ETIOLOGIC FACTORS AND REMARKS
				ONSET SYMPT.	WHEN DIAGNOSED					
Congenital Anomalies										
1	Meyer <sup>45</sup> 1859 (Quoted by R. T. Miller)	?		5 mo.	1 yr.	?	L	----	D	Congenital cystic lung
2	Miller, R. T. <sup>44</sup> 1926	?	Normal	2 wk.	5 wk.	F	R	Perm. Asp. 1 w. valve	D 5 mo.	Congen. cystic lung
3	Miller, R. T. 1926	?	Forceps. Mod. asphyxia	5 da.	5 da.	?	B	Con.	D 12 da.	Congen. cystic lung
4	Stein <sup>13</sup> 1930	?	Spontaneous	1 wk.	1 wk.	M	R	----	S	Apparently congen. cyst still present after 2 years
5	Weiner <sup>14</sup> 1930	?	Not stated		14 da.	?	L	Cont. perm. asp.	D	Congen. anomaly. Pencil thick patent bronchus opening into pl. cavity
6	Hotz, A. <sup>46</sup> 1936	1,730 Gm.	Cesarean for nephropathy. Asphyx.	5½ wk.	6 wk.	F	B	Con.	S	Congenital heart
7	Hotz, A. <sup>46</sup> 1936	3,340 Gm.	Spont. Pale on Birth	10 da.	17 da.	F	B	Con.	S	Congenital heart
8	Bertin <sup>11</sup> 1936	?	Spont. Cyanotic. Systolic heart murmur		8 da.	M	R P	Con.	D	Congenital heart. Died from pneumonia 2 mo. later
9	Miller, J. F. <sup>39</sup> 1937	?	Scanzoni	4 da.	4 da.	M	R	Asp.	D 2 da. later	Congen. abse. rt. pulm. artery, gangrene and rupture
Inflammatory Pulmonic Processes										
1	Gasul and Singer <sup>35</sup> 1933	?	Normal. Resp. rapid and sighing from birth		3 wk.	M	R	Con.	D	Rupture of abscess of lung

		Gm.	Asphyxiated	1 da.	1 da.	F	R P	Con.	S	Alveolar tear assumed. Cord around neck and enlarged thymus
22	Heijbroek, van Ebbenhorst 1936	3,930								
23	Bertin <sup>11</sup> 1936	3,660	Spont. Normal	8 da.	11 da.	F	R P	Con.	S	Unknown
24	Bertin 1936	?	L.F. Sl. cyanosis	1 da.	2 da.	M	R P	Con.	S	Ret. at 4 mo. and treated for enlarged thymus
25	Bertin 1936	?	Cesarean. Cyanosis (Previous diff. high forceps)	1 da.	1 da.	F	L P	Con.	S	Unknown. Accidental finding because of cyanosis with feeding
26	Bertin 1936	?	Difficult forceps. Asphyxia mild	?	9 da.	M	R P	Con.	S	Unknown. Accidental finding
27	Bertin 1936	3,660	L.F. epis. No asphyxia	1 da.	1 da.	F	R P	Con.	S	Unknown. X-ray taken for thymus; accidental finding
28	Bertin 1936	3,940	Spont. No asphyxia	?	1 mo.	M	B P	Con.	S	Enlarged thymus. X-ray 1st day normal. Pneumothorax at 1 mo.
29	Holz, I. <sup>10</sup> 1936	2,100	Spontaneous, 6 hr. Cyanotic, dyspnea	Birth	2 da.	?	B P	O <sub>2</sub>	S	Unknown. Malformed chest. Prominent xiphoid
30	Holz, I. <sup>10</sup> 1936	3,060	Spontaneous, 4 hr. Marked asphyxia	Birth	4 da.	?	A-B L P 4 d. R P 7 d.	Con.	S	Hypertonicity indicates birth trauma. Trachea aspirated
31	Storts and James <sup>14</sup> 1936	2,538	L.F. Epis. asphyx.	2 da.	3 da.	?	L P	Con.	S	Mouth to mouth resusc. (Died 8 wk. intussusception)
32	Hotz, A. <sup>16</sup> 1936	2,400	Spont. (A twin)	4 da.	6 da.	F	R P	Con.	S	Large thymus
33	Schuler, F. <sup>17</sup> 1938	2,840	Spont. 5½ hr. labor. Cyanosis and dyspnea	Birth	15 hr.	F	R P	----	D	Birth trauma, and cerebral hemorrhage
34	DeCosta, E. J. 1939	3,170	Spont., 4 hr. labor Sl. cyanosis	12 hr.	24 hr.	F	L P	Con.	S	Unknown, discovered in routine exam. of newborn

respiration was used. It may seem surprising that such methods were not employed more frequently in an attempt to relieve the embarrassed respiration. It must be remembered, however, that in many the babies' symptoms were so mild that they appeared only during crying and in several instances the discovery of the pneumothorax was accidental.<sup>7, 11</sup> Significant, though, is the fact that of the 14 *pneumothorax abrupta*, artificial respiration was used in 8, 57 per cent. It is difficult to determine definitely whether the pre-existing pneumothorax led to some artificial respiratory procedure or whether the attempted resuscitation produced the pneumothorax. But one must not ignore that in 57 per cent of the acute cases, artificial respiration was employed. From this it may be fair to conclude that any method of artificial respiration is hazardous and should be administered by one trained in its usage.

The fact that pneumothorax is not more frequently mentioned does not mean that it is not recognized. Failure to record cases may give the impression of rarity. For instance, in the discussion following Deissler's<sup>28</sup> brief autopsy reports of three cases of emphysema and pneumothorax following artificial respiration, Boyd and Steward mention that they have encountered several cases of emphysema and pneumothorax although they never reported them. Certain authors have witnessed from 6 to 13 cases,<sup>8, 9, 11, 46</sup> which indicates further that it is much more common than is suspected. The usual autopsy technique may not reveal the existence of such pneumothorax and many babies in which the diagnosis of atelectasis is made may have died because the lungs were unable to expand in an air-filled pleural cavity.

NOTE: Since this paper was presented, two additional cases of pneumothorax and one case of bullous mediastinal emphysema have been observed. The latter caused circulatory distress, which was relieved by aspiration of 6 c.c. of air.

#### SUMMARY

1. The literature on the subject of pneumothorax of the newborn infant is reviewed; 67 cases have been collected and studied.
2. Of these, only 46 have been directly associated with birth.
3. Two additional instances at the time of birth are reported, one unique in that subcutaneous emphysema and pneumoperitoneum were also present.
4. There appear to be two clinical types of pneumothorax in the newborn infant: one arising suddenly, *pneumothorax abrupta*, demanding prompt treatment; the other more gradual and less severe, *pneumothorax lenta*, with good prognosis irrespective of treatment.
5. Resistance to the flow of air through the tracheal catheter during insufflation is suggestive of pneumothorax.
6. The danger of producing pneumothorax by improper insufflation is stressed.
7. Pneumothorax is a condition that probably occurs much more frequently than the literature indicates. Obstetricians should be mindful of its possibility, especially when any method of artificial respiration has been employed.

I wish to express my appreciation to Dr. Louis N. Katz, Director of Cardio-Vascular Research, Michael Reese Hospital, for his encouragement and for making the animal experiments possible, and to Miss Erna Lindner for technical assistance.

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		?	Normal	4 wk.	4 wk.	?	L	Con.	D	Br. pn. and pyopneumoth.
2	Geyman and Clark <sup>36</sup> 1934									
3	Hazek (quoted by Geyman and Clark 1934)	?		7 mo.	7 mo.	?	R	Asp.	S	Acute bronchitis followed in 2 days by pneumonia (bronchial). Had measles
4	Glazer and Landau <sup>37</sup> 1935	?	Normal			M	L	Con.	D	Rupture of abscess of lung (Similar to No. 1)
5	Wilkinson <sup>38</sup> 1936	3,458 Gm.		5 da.	17 da.	M	L	Con.	D	Mult. sept. emboli, infarcts, abscess and rupture
6	Holtz, A. <sup>39</sup> 1936	?	Spont. Pale at birth, and rapid breathing	11 wk.	12 wk.	F	R	Con.	D 1 wk. later	Vitrum cordis with transp. vesicles and bronchopneumonia
7	Holtz, L. <sup>10</sup> 1936	3,300 Gm.	Spontaneous	5 wk.	6 wk.	?	L	Con.	S	Br. pneumonia—also verified by X-ray

*Recognition Later Than Ten Days*

		?	Normal	4 mo.	4½ mo.	M	L	Asp.	D	Unknown
1	Weinert <sup>40</sup> 1930									
2	Williat 1934	2,790 Gm.	Membranes ruptured early, child cyanotic	3 mo.	3½ mo.	F	R	Con.	S	Respiratory obstruction due to large thymus. Present 2 yr. later
3	Willi 1934	3,500 Gm.	Normal	1 wk.	7 mo.	F	R	Con.	S	Bronchitis
4	Engel <sup>41</sup> (Quoted by Folke)	?		1 mo.	1 mo.	?	?	----	D	Unknown
5	Riedweg <sup>42</sup> 1934	?		?	12 wk.	?	B	----	S	Pylorespasm. Pneumothorax an incidental discovery



"choked to death." The third was an occiput posterior which rotated spontaneously. Twelve hours after labor difficult breathing developed and increased until sixteen hours after delivery there was marked cyanosis, inability to swallow, and shortly afterward shock. Examination revealed: (1) absence of breath sounds on the right side, (2) suggestive hyperresonance on the right side, (3) immobility of the right chest, (4) cyanosis, (5) evident shock. X-ray showed almost complete collapse of the right lung and the heart and mediastinum displaced to the left. The treatment consisted in aspiration of air by insertion of trocar needle in midaxillary line, which permitted outrush of air with relief of symptoms. The aspiration was repeated in forty-eight hours. X-ray taken the twenty-eighth day revealed complete return of structures to normal.

I present these cases to stress, with Dr. DeCosta, the frequency of this condition and to urge that it be more frequently considered in the care of the newborn infant.

DR. FREDERICK V. EMMERT, St. Louis, Mo.—My experience with spontaneous pneumothorax in the newborn infant is limited to one case. A sextipara, aged 42 years, near term, was admitted to the hospital with profuse bleeding due to a placenta previa centralis and, as the case was also complicated by a transverse position of the fetus, cesarean section was performed. After the operation, the nurse reported that the infant appeared normal at first, but soon became cyanotic and breathed irregularly. The color of the skin was deep blue and the respirations rapid and shallow. The infant continuously emitted moaning and whining sounds. Only when oxygen was administered and external heat applied did the condition improve. An x-ray picture was taken shortly before the infant died and showed "a complete atelectasis of the right lung. The left lung was also collapsed and pushed to the midline by a large accumulation of air in the thoracic cavity. The cardiac shadow did not seem to be enlarged."

These observations could be interpreted either as a congenital anomaly such as a pulmonary fistula or as the result of traumatism. It was learned that the child had not breathed promptly and that the intern had resorted to mouth-to-mouth insufflation which, as he insisted, had been gentle. However gentle his procedure may have been, the artificial pneumothorax proved that the force of direct insufflation had been far too great for the resisting strength of the frail tissues of the lungs.

The term pneumothorax should be applied only to cases developing in the period between birth and the establishment of the normal vital processes, or to the first four or five days of life. Lesions that make their first appearance after this time may be considered as disturbances having a different cause.

In addition to the massive pneumothorax in the newborn, there occurs much more frequently a partial pneumothorax, the so-called mantle type. It is due to the escape of small amounts of air from some ruptured emphysematous blebs. The escaped air rises into the pleural cavity around the apex of the lung and hence the mantle phenomenon.

DR. DECOSTA (closing).—The discussions clearly substantiate the contention that spontaneous pneumothorax of the newborn infant occurs more frequently than the comparatively few references in the literature would indicate. This paper has been presented with the hope that awareness of this condition will lead to its recognition, and thereby permit appropriate treatment.

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## DISCUSSION

DR. J. MILTON SINGLETON, KANSAS CITY, MO.—I have an additional case to report. This patient had had two previous spontaneous abortions at four and four and one-half months, respectively. Labor came on prematurely at eight months, was tumultuous, and the baby was resuscitated with considerable difficulty. The baby was cyanotic, and when it cried cyanosis grew deeper. A film showed the line of collapsed lung and an outer area where there are no lung markings. X-ray taken after four or five days revealed that the area of pneumothorax had transferred to the other side.

The physical findings, absence of breath sounds, and hyperresonance confirmed the diagnosis. This case was of the mild type and responded to oxygen inhalations given several times daily over a period of ten days. X-ray taken on the fourteenth day revealed complete absorption of air.

In addition to this case, I have the privilege of reporting two others from Dr. Pakula's service.

CASE 1.—This was a full-term male infant. The labor had been induced and delivery was accomplished from the O.L.P. position by low forceps after twenty and one-half hours of difficult labor. The mother had received nembutal, scopolamine, and morphine. The child breathed only after 1.5 c.c. of coramine had been injected into the cord vessels, and oxygen and carbon dioxide given. Cyanosis persisted and the pulse and heart beat continued feeble. Physical findings were typical and the x-ray revealed the Mantle type of pneumothorax with persistence of the fold. No aspiration was done. Treatment was continued for fourteen days. X-ray and physical examination revealed complete absorption of air.

CASE 2.—This was a full-term male, delivered six and one-half hours after onset of labor in a third pregnancy. The first pregnancy had terminated in a stillbirth. The second baby died eight hours after delivery and was said to have

and intertrigo. Maylard made the interesting discovery that the rectus muscle could be sectioned with impunity when he found it necessary to enlarge his field of operation transversely after first having made a longitudinal incision. The transverse scar showed perfect healing while the longitudinal wound subsequently developed an incisional hernia. Following this incident, he began to use transverse incisions with complete section of the rectus muscles. He published his report in 1907.

In this country Stimson of New York was one of the first to use this type of transverse incision. In 1904 he published an analysis of 150 operations in which this incision was used. Boeckmann advocated transverse incisions for all abdominal operations in 1910, and gave excellent reasons for doing so. Sloan used the Pfannenstiel incision with modifications regularly from 1909 on. He stated that he is convinced of its superiority to the longitudinal incision because the dangers of postoperative hernia and of separation of wound margins are eliminated. Tovey thinks that the infrequent use of the Pfannenstiel incision in this country is probably due to the fact that it has rarely been properly described. In a personal communication to the author, Quain states that after seeing the satisfactory results in nearly 3,000 cases of transverse incision, he is more convinced than ever of the definite advantages over other more destructive incisions. During recent years there have been very few references to the use of the transverse incision in pelvic surgery in the American literature. Most of the current reports still originate in foreign countries.

#### ANATOMY

The anatomy of the abdominal wall will be reviewed briefly because anatomic considerations are the most important reasons for doing the transverse incision.

The abdominal wall consists mainly of a cylindrical sheet of voluntary muscles. The most important of these are the three aponeurotic transverse muscles—the external and internal oblique and the transversus abdominis. These aponeuroses fuse to form the anterior and posterior sheaths of the rectus muscles, and then pass medially to form the linea alba. The rectus muscles are longitudinal bundles divided by three or four strong transverse tendons into independent muscular masses, each of which has its own motor nerve supply. Thus, contractions may be considered segmental. This muscle layer is surrounded by a distinct sheath of fibrous tissue, the anterior layer of which is known as the deep fascia of the abdominal wall. The posterior layer is referred to as the transversalis, or endo-abdominal fascia, and is too often disregarded in a repair of the abdominal wall. Superficial to the so-called deep fascia is a layer not unlike the superficial fascial layer, the subperitoneal fibroareolar layer.

The nerves have a more or less transverse direction while the blood vessels and lymphatics course longitudinally. The blood supply of the abdomen as a whole is rich except for the linea alba which is *practically nonvascular and equally destitute of lymphatics*. Since a well-healed wound depends upon the absence of tension between the freshly united margins of the wound, a good blood supply to and from the parts, and a ready absorption of exudates by means of abundant lymphatics, it is clear that the midline of the abdomen possesses these requisite conditions less than any other part. Conversely, if we consider the line to which these requirements are fulfilled to the utmost extent, it must course more or less transversely. Unlike the median incision, the transverse does not separate the aponeurosis crosswise, and contractions of the oblique and transversalis muscles do not exercise tension on the margins of the wound. Contractions of these muscles rather serve to bring the wound edges together.

Considering complete transverse division of the rectus muscles, one might presume that this procedure would leave a weakened abdominal wall or defective scar. This presumption is not supported by evidence. When a rectus muscle is divided, its fibers naturally retract but only to a very limited extent because of

# TRANSVERSE ABDOMINAL INCISIONS IN PELVIC SURGERY\*

## A REPORT OF SEVEN HUNDRED CASES

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(From the Fargo Clinic)

THIS study was prompted by the impression that lower abdominal transverse incisions are not widely used throughout this country. The writer was schooled to do longitudinal incisions, but upon observing the results in routine transverse incisions has become convinced that the latter are the most logical approach to pelvic pathology when laparotomy is indicated. I sent out a questionnaire to several leading gynecologists in the United States, and it was found that all but a few do not use the transverse incision or use it in less than 1 per cent of their operative cases. For the infrequent use of the transverse incision, these men gave various reasons. Among them were satisfaction with the midline incision, the greater danger of infection and the poor exposure with the transverse incision, or the opinion that this incision is illogical. In this study an attempt will be made to answer these objections and to cite the advantages of the transverse abdominal incision over the median or paramedian approach. A report of the results in 700 consecutive cases will be made.

### HISTORY

Theodore Kocher was one of the first surgeons to try to find a substitute for longitudinal incisions in laparotomies. Reasons for this search were esthetic considerations and the desire to avoid postoperative hernia. He stated that one would get "beautiful" scars if the skin were incised along Langer's lines of cleavage. At the International Congress in Geneva in 1896, Küstner and Rapin recommended transverse incisions of the skin at or below the margin of the pubic hair. The skin was opened transversely, and the other structures were divided longitudinally as usual. Through the resulting small opening in the abdominal wall, pelvic surgery could be performed to a limited extent only. In 1900, Pfannenstiel of Breslau presented an extensive paper on the advantages of the suprapubic transverse incision of the fascia in gynecologic laparotomy. He had previously cultivated the vaginal route but had given it up because of poor exposure. His original resort to the vaginal approach was prompted by the high incidence of hernias and bad scars. He claimed that in order to remove these two principal objections to longitudinal laparotomies, he made his skin incision after the custom of Küstner-Rapin following which he made a transverse incision in the entire width of the anterior sheath of the rectus muscles. He stated that the Küstner-Rapin incision is esthetically ideal, but that it does not protect against hernias any more than the longitudinal incision does, since hernias result from defective healing of the fascia or aponeurosis, while perfect healing of the skin does not afford any protection.

Another early proponent of the transverse incision was Wanschler of Denmark, who added a new inducement for Pfannenstiel incisions for the purpose of excising some of the skin and superficial fat on women with pendulous abdomens

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level of the incision may vary, depending upon the size and situation of the pathology. It is possible to extend the curve of the incision as far as the anterior superior spines of the iliac crest, forming a convex line with the middle of the incision near the upper border of the pubis, the two upper extremities on a level

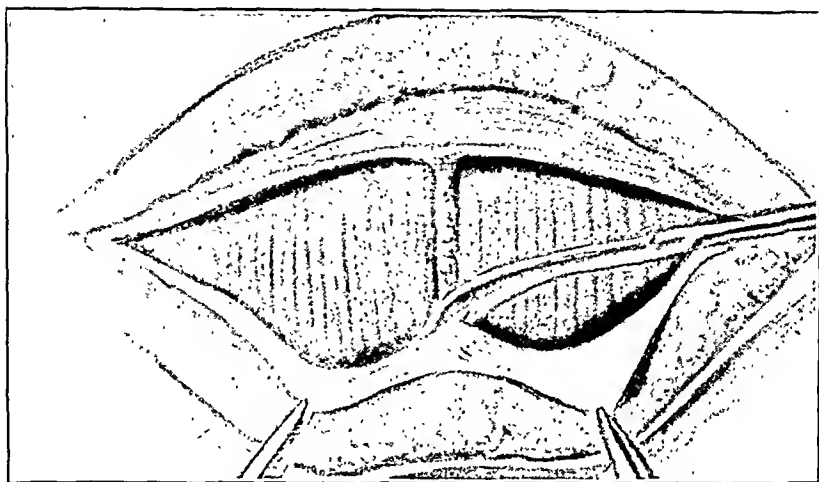


Fig. 3.—Pfannenstiel incision. The anterior sheaths are dissected superiorly and inferiorly to free the recti and allow their subsequent retraction.

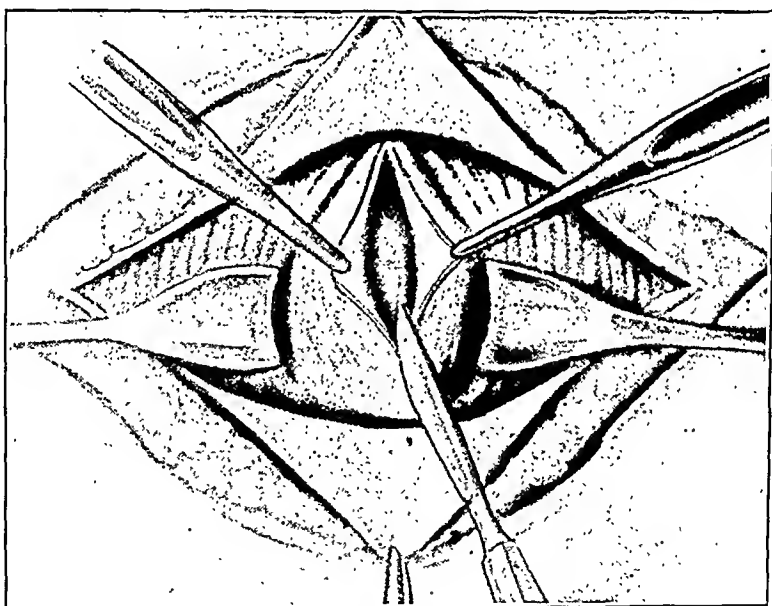


Fig. 4.—Pfannenstiel incision. The recti are drawn laterally and then their anterior sheaths are retracted superiorly and inferiorly; a vertical incision is made in the posterior sheath, which at this level consists of transversalis fascia, extraperitoneal fat, and peritoneum.

with the upper portion of the abdominal pathology. Close proximity to the pubis in the region of the mons veneris is inadvisable because of the possible cutaneous displacement with the scar falling on the upper edge of the superior ramus of the os pubis, leading to a painful pressure upon the scar region.

In the Maylard or Bardenheuer incision, the skin, subcutaneous fatty tissue, and fascia are incised at a suitable level, usually halfway between the umbilicus and pubis. The anterior sheath of the rectus is not separated from the

its segmental nature. In the presence of healing, the rectus muscle forms an adventitious linea transversa which is particularly firm.

If we keep these anatomic relations in mind, we must conclude that, whenever an abdominal incision is made vertically or parallel to the long axis of the body, those structures which give the principal support and tone to the abdominal wall are being injured, that is, functionally impaired.

### TECHNIQUE

There are two types of abdominal transverse incisions used in pelvic surgery, the Pfannenstiel and the Maylard (Fig. 1). Graves has referred to a Bardenheuer incision which is essentially the Maylard technique.

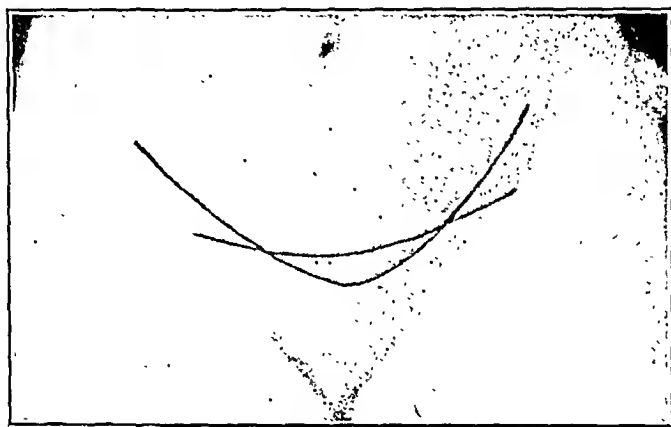


Fig. 1.—Pfannenstiel incision and modification. The Maylard may be made along the same lines by merely severing the recti.

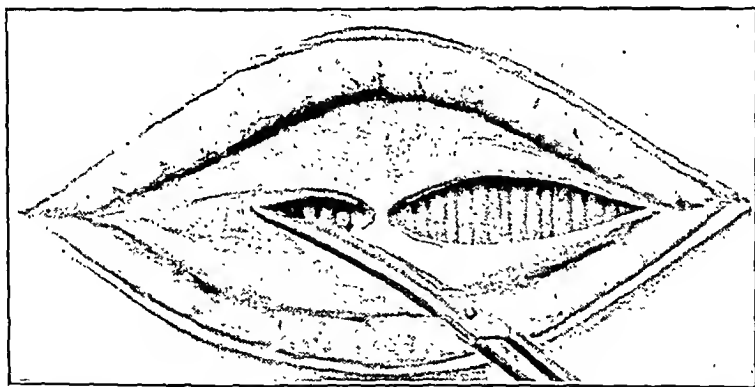


Fig. 2.—Pfannenstiel incision. Transverse incision is carried through the skin and the anterior layer of the rectus sheath.

The Pfannenstiel incision, like the McBurney, is to be regarded as a muscle-splitting operation. As originally described by Pfannenstiel, the skin, subcutaneous fatty tissue, and fascia were transversely severed about 4 cm. above the symphysis in an extension of 10 to 20 cm. (Fig. 2). This incision may be extended on either side by a curved incision in an upward direction, similar in shape to the transverse uterine incision used in lower segment cesarean section. The fascia is separated from the rectus muscles in upward and downward directions (Fig. 3). The rectus muscles are then separated and retracted laterally. The transversalis fascia is opened, and the peritoneal cavity entered (Fig. 4). The

longitudinal incisions were made with 14 postoperative hernias, giving percentages of 0.38 and 7.86, respectively. It is worth stressing that out of 794 patients operated upon according to Pfannenstiel's technique 45 healings were complicated by infection but that the occurrence of hernia was avoided. Evisceration was completely avoided. From this, one would conclude that the incision was an important factor, particularly in the cases of wound infection. Peiro reports that not a single hernia occurred in 750 transverse operations.

Hartzell and Winfield, in a very thorough collective review on disruptions of abdominal wounds, state that this complication occurs in about 2 per cent of the cases. Quoting them further: "Many partial wound disruptions undoubtedly go unrecognized and frequently give rise to incisional hernias. Although the major effect of this catastrophe in many instances is an increase in the morbidity alone, the mortality nevertheless is extremely high, being variously quoted from 20 per cent to 75 per cent. . . . We feel that the evidence tends to militate against vertical abdominal incisions, and, therefore, urge the use of transverse

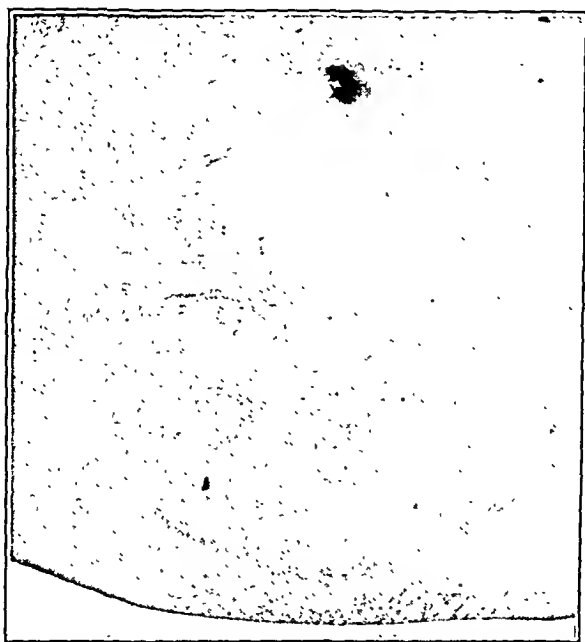


Fig. 5.—Right rectus and Pfannenstiel scars. When one encounters these incisions in the same individual, he sees how nicely the transverse incision heals by comparison. The rectus incision was done three years ago for acute appendicitis. The Pfannenstiel incision was done one year ago to relieve ruptured ectopic pregnancy.

and oblique muscle- and fascia-splitting incisions whenever possible. . . . During the past two years, we have become more and more inclined to the use of transverse or muscle-splitting abdominal incisions, and it is gratifying to note that not a single case of disruption has occurred in this group of cases. . . ." In summarizing they state that "consensus of opinion would indicate that wound disruption is essentially a complication of the vertical incision."

Why then do we adhere to the midline incision? Perhaps for the same reason that some of us cling to myths, such as, belief in the value of certain glandular extracts proved to have no biologic potency or the impression that two strands of catgut will give firmer wound healing than one. We are reluctant to change our habits.

*Better Scar.*—The desire to have better looking scars first prompted the older surgeons to use the transverse incision. Recently Conway

rectus fibers. The transverse incision is then carried directly through the rectus muscles down to the posterior sheath or transversalis fascia which is incised along with the peritoneum transversely.

In this review, different sizes and types of catgut were used in the repairs. However, in view of various studies, particularly Bates' investigation and Howes' work on tensile strength of catgut, the author now uses zero or finer gauge chromic throughout. Pfannenstiel incisions are closed in the following manner. Peritoneum and transversalis fascia with continuous suture; rectus muscles loosely approximated with continuous suture; the deep fascia with continuous suture which is re-enforced with interrupted sutures at intervals of 2 to 3 cm., and the skin is closed with medium or fine dermal. Stay sutures are not used routinely.

Maylard incisions are closed in the same manner, except that the rectus muscles are not sutured. Though some have held it necessary to suture the rectus muscles to the anterior sheath either before or after severing the muscle, experience has definitely refuted this view. The retraction of muscle fibers is insignificant. Approximation of the edges of the anterior sheath is sufficient to obtain good muscle healing. In certain individuals silkworm gut sutures may be advisable.

#### ADVANTAGES

*Almost Complete Absence of Postoperative Hernia and Evisceration.*—One is indeed impressed by the number of articles which have appeared in the last five years on incisional hernia and disruption of abdominal wounds. Furthermore, one's attention is drawn to the fact that almost all of these complications occur in longitudinal incisions. This fact in itself should be of sufficient importance to direct interest to the transverse incisional approach to the abdomen.

It is my firm conviction that the direction of the incision is the most important factor in prevention of these complications. Whatever the factors concerned in the production of hernia, section of the rectus muscle transversely is not a significant one. McNealy states that experimental and clinical investigations strengthen the impression that the transversalis fascia is the most important tissue concerned in preventing the development of any type of direct hernia.

Southam reports that 2 per cent of 29,000 operations were done for postoperative hernia. Coates reported a series of incisional hernias with a preponderant number occurring in paramedian and median incisions. In speaking of these, he concludes that they are not anatomically sound from the point of view of easy healing although necessary for exposure in some cases. Hepburn reports that wounds in the lower midline are apparently unduly susceptible to rupture. He feels that the frequency and seriousness of postoperative ventral hernia and the suffering which its victims undergo make this complication one of the major surgical problems.

In an analysis of 3,142 cases of hernia at Peter Bent Brigham Hospital, Branch reports that 9.5 per cent were incisional. In this series, 45.3 per cent were found to occur in lower midline incisions. Stated differently, incisional hernia occurred in practically one out of every 20 lower midline incisions. Can one fail to be arrested by this appalling figure when one notes that incisional hernia occurs in much less than 1 per cent of transverse lower abdominal incisions? (Pietro, Gianella, Sarwey, Hartzell and Winfield.)

Gianella, quoting Abel, reported that, in 9.8 per cent of the cases healing by first intention, hernia occurred where longitudinal incision was used. Abel made this deduction from extensive material. In 794 of Gianella's cases of the Pfannenstiel incision, 3 postoperative hernias occurred. During this period, 178



it was relatively common in longitudinal openings. Furthermore, in many instances the laboriously united peritoneum had torn open. The higher incidence of adhesions in longitudinal openings is perhaps due to the increased lateral tension accompanied by the greater difficulty in peritoneal closure and the subsequent migration of the omentum to the wound site. In an experimental study Quain showed that disturbance of the nerve supply plus trauma or irritation predisposes to adhesions.

Sloan, in describing the requisites for prevention of adhesions, states: "It is of prime importance that an abdominal incision be used that does not destroy the nerve supply of any portion of the peritoneum and that can be closed without tension upon the sutures in contact with, or through, the peritoneum. This obviously cannot be done unless the fascia fibers remain intact. The transverse incision meets this requirement and also gives ample exposure."

*Adequate Exposure.*—When a vertical incision is made, the open wound must be stretched into a transverse aperture; with the transverse incision, such distortion is unnecessary and the exposure generally better. Occasionally the Pfannenstiel exposure may be considered inadequate and then the Maylard may be used. In fact, the transverse incisions may be made at any level. With the Maylard incision, the necessity for retraction is diminished and tissue trauma is less.

To those who argue that exposure is inadequate and more difficult with transverse incisions, I would urge that after all our purpose in gynecologic surgery is to expose the uterus, tubes, and ovaries. When the transverse incision is used, the pathology lies directly beneath the incision, and as a result, since there is less manipulation of the viscera, such complications as ileus are rare. In doing the low cervical cesarean section with transverse incision in the uterus the Pfannenstiel gives particularly good exposure.

The objection has been offered that the transverse incision cannot be extended to the upper abdomen to take care of possible gall bladder or stomach pathology. One does not often meet a situation where this would conceivably be necessary. The gall bladder can be palpated and the appendix removed easily through both the Pfannenstiel and Maylard incisions. Two good incisions are infinitely better than one poor one, should exposure of another portion of the abdominal cavity seem advisable.

One must, of course, decide whether the Pfannenstiel or Maylard is needed. Such a decision may be made at the beginning of the operation merely by making a small opening in the peritoneum before separating the rectus from its anterior sheath. In most of the cases this procedure will not be necessary, however, as one is usually able to outline the pathology through bimanual examination. When the Maylard incision is made, the exposure is excellent. The closure is easier because there is less gaping and little tension.

*The Absence of Lateral Tension on Scar.*—Whipple and Elliott recognize the importance of lateral pull of the oblique and transversalis

made a study of cutaneous healing in wounds. He emphasized the importance of placing the long axis of an incision parallel to Langer's lines of elasticity of the skin whenever possible. In his study, he came to the conclusion that the lines of elasticity of the skin run transversely in the suprapubic area rather than obliquely vertical as Langer's diagrammatical figure reports them. Photographs of healed wounds would tend to bear out Conway's conclusion. One has only to observe scars of longitudinal and transverse incisions on the same individual to be convinced of this fact (Fig. 5).

It may be argued that incisions in this region are not ordinarily displayed and that their appearance is a small matter. However, the esthetic viewpoint may not be disregarded. The thought of a hideous scar may conceivably restrain some from necessary surgery. It is frequently said that the patient judges the surgeon's handiwork by the scar.

*Better Blood Supply to Wound.*—A common objection to the transverse incision is increased bleeding. This very bleeding, however, speaks for the definitely better blood supply to the transverse wound—hence, for better healing. Albin stresses the poor nutritional condition of the wound as a factor in wound disruption. We know the blood supply is poorest in the midline, the most avascular region in the abdomen. It is made up of tissues of the least vitality. This results in a slower healing and, as many studies have proved, predisposes to postoperative hernia and evisceration.

The inferior epigastric vessels need not always be severed in the Maylard incision. However, if it is necessary to cut these vessels, the anastomoses are so numerous that the area does not suffer.

Because of the improved blood supply to the scar, there is more rapid healing and consequently quicker recovery. From an economic standpoint this is exceedingly important. Most surgeons keep patients who have had midline incisions in bed from ten to fourteen days. Those who have had Pfannenstiel incisions may get up safely as early as the fourth or fifth postoperative day, depending upon the extent of the surgery and the type of patient. Naturally, certain patients must remain in bed much longer.

*No Division of Important Nerves.*—There is likewise no division of important nerves when the median incision is used. However, in a transrectus longitudinal incision the tissue medial to the wound may suffer. In a transverse incision there is little danger of disturbing the nerve supply since the direction of the incision is parallel to the nerves. Heaney offers the objection that the pubic area is frequently anesthetic as a result of the transverse incision. With this objection in mind patients were questioned concerning presence or absence of sensation in the pubic area. Not one instance of anesthesia was noted. It is probable that it may occur when the incision is made too close to the symphysis.

*The Tendency to Adhesions Is Greatly Diminished.*—Sprengel was the first to draw attention to this. He noted when doing autopsies that it was rare to find omentum adherent to a transverse incision, whereas

TABLE II. OPERATIONS

<i>On uterus:</i>		
Suspension		214
Gilliam		172
Baldy-Webster		8
Olshausen		1
Coffey		2
Unspecified		31
Myomectomy		47
Supravaginal hysterectomy		104
Complete hysterectomy		53
Hysterotomy		2
<i>On adnexa:</i>		
Removal of one tube		112
Removal of both tubes		85
Sterilization		62
Plastic		12
Removal of one ovary, ovarian cyst, or parovarian cyst		177
Removal of both ovaries or bilateral ovarian cysts		30
Ectopic pregnancies		15
<i>Miscellaneous procedures:</i>		
Appendicectomy		355
Herniotomy		3
Presacral resection		4
Meckel's diverticula resection		3
Synechtenterotomy		29
<i>Additional procedures done at one or more of the above operations:</i>		
Dilatation and curettage		67
Lipectomy		5
Hemorrhoidectomy		5
Operations on cervix		27
Repair of cystocele		6
Repair of rectocele		16

TABLE III. POSTOPERATIVE COMPLICATIONS

<i>Pulmonary</i>		
Embolism	6	0.85%
Pneumonia	2	0.28%
Upper respiratory infection	6	0.85%
Pleurisy	1	0.14%
Intestinal obstruction	1	0.14%
Gastric dilatation	1	0.14%
Thrombophlebitis	12	1.7 %
Wound infection	26	3.7 %
Peritonitis	9	1.28%
<i>Genitourinary</i>		
Cystitis	4	0.57%
Vesicovaginal fistula	1	0.14%

## DISCUSSION

Seven hundred consecutive cases of transverse incision are reviewed. A preponderant number (96.1 per cent) of these cases were of the Pfannenstiel type. The Maylard incision was used in 3.9 per cent of the cases, or about once in twenty-five. These figures emphasize the fact that the Pfannenstiel may be used for most pelvic abdominal

muscles in vertical incisions. Shipley states that a very important point is the transverse direction of the deeper layers of the abdominal wall, giving poor support to the suture line of a vertical incision.

The body and strength of the abdominal wall are made up of three lateral and superimposed muscles, the external and internal oblique and the transversalis. These muscles have been described above, but I should like to reiterate that the one broad tendon of these flat muscles unites at the midline with its partner of the opposite side. The function of these muscles is to pull outward and backward from the midline in front in order to increase the intra-abdominal pressure. Thus, opening the abdomen at the midline in the long axis of the body severs the structures which give the chief support and tone to the abdominal wall, placing a definite lateral pull on the incision.

Sloan has worked out a rule for estimation of the tension upon the suture line, following a longitudinal incision. "The longer the longitudinal incision the more force is required to bring the ends of the fibers of the divided aponeuroses together. The force required increases in proportion to the square of the length of the incision. . . . The lateral pull upon the suture line following a longitudinal abdominal incision is in proportion to the square of the length of the incision. . . . So far as we have been able to determine, when complete relaxation is not present, the lateral abdominal tension is about thirty times as great as the vertical. If this is correct, the strain upon the suture line of a longitudinal incision is thirty times as great as that upon the suture line of the transverse incision."

Farr calls attention to the fact that tension on transverse wounds can be lessened by simple posture change. He states that vertical wounds are constantly under tension—every hour of the day as long as the patient lives. If early hernia is avoided, the danger of its subsequent development remains, as scar tissue under strain will gradually lengthen and weaken.

*Lower Morbidity and Mortality.*—With an almost complete absence of evisceration and incisional hernia, the mortality and morbidity are necessarily lower. It is difficult to get figures of similar studies for comparing the incidence of wound infection. Hughson reports 5 per cent wound infection in a series of operations for inguinal hernia. Beekman reports 4.9 per cent wound infection in a study of complications following hernia repair. Curtis and others have held that infections in transverse wounds have more serious consequences. I might say the studies of Abel, Boeckman, and Sloan who have actually used the incision tend to refute this contention. It is my impression from data gleaned in this study that other complications are generally lower when transverse incisions are used.

## DATA

TABLE I. GENERAL INFORMATION

Number of operations	700	
Pfannenstiel	673	96.1%
Maylard or Bardenheuer	27	3.9%
Mortality	13	1.8%
Unsatisfactory follow-up	130	18.6%
Stay sutures	180	25.7%
Vaginal drains	26	3.7%

4. Aged 30 years. Bilateral salpingo-oophorectomy. Bilateral hydrosalpinx and ovarian cysts. Died second day postoperatively of shock (?).

5. Aged 27 years. Suspension and appendicectomy for retroversion and recurrent appendicitis. Developed a bronchitis second day postoperatively. Diagnosis of intestinal obstruction on fifth day. Re-operated. Enterostomy done. Died two days later.

6. Aged 27 years. Hysterectomy for fibrosis uteri and membranous dysmenorrhea. Died ninth postoperative day of peritonitis.

7. Aged 44 years. Bilateral salpingectomy and appendicectomy. Bilateral pyosalpinx. Ovarian cyst excised. Died fourth postoperative day of peritonitis.

8. Aged 52 years. Panhysterectomy for fibroid uterus. Had a secondary anemia. Died of peritonitis on the eighth postoperative day.

9. Aged 40 years. Supravaginal hysterectomy. Right salpingo-oophorectomy for fibroids. Melanosis of adrenals. Died third day postoperatively of Addison's disease.

10. Aged 56 years. Panhysterectomy. Carcinoma of cervix. Died ninth postoperative day of peritonitis.

11. Aged 35 years. Bilateral salpingo-oophorectomy. Bilateral pyosalpinx. Died of peritonitis on second day postoperatively.

12. Aged 43 years. Exploratory laparotomy. Myxosarcoma. Died of metastases on eighty-sixth postoperative day.

13. Aged 45 years. Tubo-ovarian abscess. In hospital thirty-seven days before surgery. Died of cardiac failure on eighth postoperative day.

The cases of peritonitis occurred in patients who had hysterectomies or infected tubes. Five patients died of peritonitis, this being the most frequent cause of death.

The patients who died of metastatic carcinoma and myxosarcoma died on the fortieth and eighty-sixth postoperative days, respectively. Perhaps these may be properly excluded as nonoperative deaths. However, they are included in the statistics.

There were 418 operations on the uterus, most of them suspensions. The Gilliam suspension was used most frequently. The appendix was removed in 355 or slightly more than 50 per cent of the cases. The results indicate that the appendix may be safely removed in the average uncomplicated pelvic operation. It should not be electively removed in salpingitis, acute or chronic. The patients who had multiple procedures suffered a higher incidence of postoperative complications and generally required longer postoperative stays. The vesico-vaginal fistula occurred following panhysterectomy for malignancy. Four instances of pulmonary embolism occurred in patients who were also diagnosed as having a thrombophlebitis. In at least two of these, the embolism occurred before there was evidence of phlebitis. None of these cases of pulmonary emboli was fatal.

Since this is a study primarily of transverse incisions and not of mortality and morbidity as limited to respective operations, a more detailed analysis is not given.

#### SUMMARY

1. Transverse abdominal incisions for pelvic pathology are not widely used in this country as revealed in answers to a questionnaire I sent out.

2. In my opinion these incisions are the safest and most logical approach to pelvic pathology when laparotomy is required.

surgery. However, when the Maylard was used, there was no instance of impairment of wound healing, no evidence of failure of the ends of the rectus muscles to unite, and no instance of hernia or evisceration.

The incidence of wound infection in this series is 3.7 per cent. Of course, infection itself is not dependent on the direction of the incision. Our statistics indicate, however, that infection is considerably lessened by the transverse incision, the probable reason being the increased blood supply to the area which enables the tissues to combat infection more efficiently. Wound infections in transverse incisions certainly do not hold the serious consequences, namely markedly increased possibility of hernia or evisceration, that longitudinal incisions do.

Thrombophlebitis occurred in 1.7 per cent of the cases. This may strike some as high. However, it must be remembered that this study concerns only abdominal gynecologic operations. Hampton and Warburton found the incidence of thrombophlebitis to be 1 per cent in a study of 21,000 gynecologic operations at the Johns Hopkins Hospital. Eighty-one per cent of the cases of this complication occurred in abdominal operations. Hence, if one were to ascertain the incidence in terms of abdominal operations, the determinations would be considerably higher.

In evaluating general postoperative discomfort, it is difficult to make unbiased observations, but I should say that patients who have had transverse incisions complain less. They are certainly allowed to leave their beds earlier and return to physical work sooner.

Of the patients, 81.3 per cent had adequate follow-up in return office visits. Many of the remaining 18.7 per cent were referred back to their local physicians for subsequent care. It is likely that if any patient had developed a hernia she would have been reported. However, none was called to our attention. Nevertheless, the figure of 570 cases with adequate follow-up, revealing no evidence of post-operative hernia, is impressive. None of the 700 cases developed the slightest degree of wound disruption.

Stay sutures were used in 25.7 per cent of the cases. The fact that approximately three-fourths of the cases did not have stay sutures would add to evidence of others that they were not an important factor in prevention of wound disruption. I feel that they are not indicated in clean cases, but may be advisable when infection is known to be present.

The mortality rate was 1.86 per cent, 13 patients having died during the postoperative stay. Briefly they were as follows:

1. Aged 23 years. Patient apparently in good health. Operated upon for recurrent appendicitis and retroversion. Anesthesia death during operation.
2. Aged 47 years. Exploratory laparotomy. Carcinoma of ovary. Died on the fortieth postoperative day of metastatic carcinoma.
3. Aged 33 years. Supravaginal hysterectomy for fibroids. Pneumonia. Died on the sixteenth postoperative day.

## DISCUSSION

DR. W. O. JOHNSON, LOUISVILLE, KY.—Dr. Hunter's presentation of 700 transverse incisions with a mortality rate of 1.86 per cent and a lessening of upper respiratory infections is convincing. Anatomically there is no doubt that the transverse incision is a superior incision.

One limitation to the transverse incisions is found in the patients with poor abdominal support caused by diastasis of the rectus muscles, from repeated pregnancy or multiple, large tumors. In such cases, I believe that the longitudinal incision should be used to approximate the recti in the midline. In the obese, thick-walled abdomen, the transverse incision is far more satisfactory and results in fewer wound avulsions.

One outstanding objection to this incision is that it takes time. This cannot be a real objection because it saves time in the major portion of the operation, by facilitating more adequate exposure.

Another possible objection to the transverse incision is the possible dissection of infection into dependent parts of the fatty tissue in infected cases, which may necessitate incision later for dependent drainage.

DR. GILBERT F. DOUGLAS, BIRMINGHAM, ALA.—I have used this incision for twenty years, and I have never seen a postoperative hernia in these cases.

There are just a few points that we must keep in mind in using the Pfannenstiel incision. First, we must expect to get a little more serum oozing than in a midline incision. To obviate that we leave a piece of rubber dam in the fascia for twenty-four to forty-eight hours. Second, there is some limitation as to the size of the tumor for which it may be used. Any fibroid up to the size of a three and one-half to four months' pregnancy can be removed easily through a Pfannenstiel incision.

DR. JOHN M. WAUGH, ROCHESTER, MINN.—Dr. Heaney expressed the belief that anesthesia over the pubic region frequently results from transverse incisions. This might be anticipated, as the terminal branches of the nerves could readily be severed, because they tend to run superiorly and inferiorly rather than parallel to the fibers of the external oblique muscle. Lymphatic drainage of the lower part of the abdomen is from the umbilicus downward toward the inguinal and pubic regions. Thus, the lymphatic vessels would be severed by any transverse incision and lymphatic drainage would be blocked. Incision in the median line interferes less with nerves and with blood and lymph vessels than does the transverse incision. Dr. Hunter's statement that the linea alba is almost avascular is true, but since it is practically a tendon, it requires less blood than does a muscle, which has work to perform by contraction of its fibers. This does not mean, however, that the tendon has less recuperative power than has muscle. On the other hand, repair of tendon and fascia is faster than repair of muscle because the latter is a more specialized tissue.

If, according to McNealy, the transversalis fascia is the most important tissue concerned in preventing the development of any type of direct hernia, certainly the Pfannenstiel incision is no improvement over the usual incision low in the median line, for in both incisions the transversalis fascia is severed in the same longitudinal axis.

In almost four-fifths of Dr. Hunter's cases, the uterus was not removed and some type of conservative pelvic procedure was performed which, of course, would help to explain the effectiveness of the Pfannenstiel incision in his group of cases as deep pelvic exposure was not often required. He found it necessary to resort to the Maylard incision only twenty-seven times, and it is possible that in a larger series of cases in which the latter incision was employed some weakness might become apparent.

All surgeons have seen incisional hernias develop, even in a McBurney incision made for appendectomy, and it is only reasonable to assume that such hernias will follow the Pfannenstiel incision when and if it is used as widely as the McBurney incision is employed. Certainly it must be agreed that because of the different axes of the incisions in the anterior sheath of the rectus and transversalis muscles

### 3. The following advantages of this type of incision are stressed:

A. Almost complete absence of postoperative hernia and evisceration. Careful review of the literature reveals that these complications are essentially those of unphysiologic incisions, that is, incisions other than transverse.

B. Better scar. Incisions should be made along Langer's lines of skin cleavage.

C. Adequate exposure. The Pfannenstiel can be used in a preponderant number of cases and when one is familiar with this incision, he can usually get adequate exposure. The Maylard or Bardenheuer incision will give adequate exposure for any pelvic operation.

D. Better blood supply to wound with consequent better wound healing and lower incidence of wound infection.

E. Less tendency to adhesions. Some factor other than imperfect closure is responsible for the high incidence of adhesions following longitudinal incision.

F. Absence of lateral tension to wound.

G. Diminished morbidity and mortality with a shorter hospital stay and earlier return to physical work.

### 4. Seven hundred cases of transverse incision are reported without one instance of postoperative hernia or evisceration.

I wish to express my appreciation to Dr. N. Tronnes for suggestions and to other members of the Fargo Clinic, Fargo, N. D., for permission to use their cases in the preparation of this study.

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# SCARLET FEVER IN OBSTETRICS\*

## REPORT OF AN EPIDEMIC

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EPIDEMICS of scarlet fever among obstetric patients are rare, and in no instance has an outbreak in this country been studied by modern bacteriologic and epidemiologic techniques. For these reasons it has seemed advisable to present the details of such an epidemic which occurred during the last winter (1938 and 1939) in a maternity service connected with a large general hospital.

The obstetric service of the University Hospitals receives patients (largely indigent) from all parts of the State, which has a total area of 56,147 square miles, and a population of approximately two and one-half millions. Prenatal supervision is given by local physicians until one to two weeks before the expected date of delivery. Admissions to the obstetric service vary from 120 to 175 each month. Physical conditions are such that considerable overcrowding is inevitable, and the danger of spreading contagious diseases is increased.

### EPIDEMIOLOGY

Apparently the streptococcus involved in the epidemic was introduced into the ward by Mrs. H. C. (1), who was admitted on Dec. 17, 1938, with a near term pregnancy, an acute bartholinitis, and a severe upper respiratory infection of one week's duration. She presented a moderate cervical lymphadenopathy, but was afebrile. Three weeks later it was learned from relatives that she had been exposed shortly before admission to an individual in the prodromal stage of scarlet fever. The Bartholin abscess was drained on December 19. The patient was segregated in a two-bed ward where she was in contact first with Mrs. W. (2) overnight, and later with Mrs. P. (3), who also had a severe upper respiratory infection. On January 1, Mrs. H. C. (1) was delivered by low midforceps under local anesthesia supplemented by ethylene. On the following day her temperature rose to 102.4° F., and the pulse rate was 142 per minute. At this time she developed an acute laryngitis with almost complete aphonia. The temperature and pulse remained elevated, and the patient was isolated two days later, at which time it was learned that vaginal cultures contained gonococci and beta-hemolytic streptococci. This patient eventually developed a clinical, generalized peritonitis and was acutely ill for three months. When discharged at the end of four months, she was still incapacitated but free from fever. At no time during her illness was there any evidence of rash or desquamation.

The first case of scarlet fever appeared Dec. 25, 1938, in Mrs. F. (4), who had been admitted to the hospital Nov. 21, 1938, and had delivered December 19. Mrs. W. (2), who had been in the room with Mrs. H. C. (1) and later in the labor room with Mrs. F. (4), showed a rhinitis on December 26, delivered spontaneously on December 29, and later that day showed clinical scarlet fever. On Jan. 3, 1939, two ward nurses (5 and 6) and one staff member (7) presented sore throats.

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in the Pfannenstiel incision, the danger of evisceration should be less than when incision is in the median line. The Maylard incision does not have this advantage, however, as all layers are cut in the same axis.

In the last five years, at the Mayo Clinic, we have used the low transverse type of incision only two or three times in approximately 5,000 gynecologic laparotomies. The incision in the low median line has proved satisfactory and the incidence of hernia and evisceration is very low. I believe that either hernia or evisceration occurred in considerably less than 1 per cent of the patients. We feel that in making the incision low in the median line, it is important to open both sheaths of the rectus muscles, thus giving, in closure, the effect of three layers (peritoneum and transversalis fascia, rectus muscles, anterior sheath). Incision low in the median line seems to us to give better exposure and to require less time and cause less trauma in the making than does the transverse incision.

I would like to ask Dr. Hunter whether the follow-up study which he made in regard to hernia was conducted by letter or by personal examination. Also, was exposure with the transverse incision adequate for removal of huge fibromyomas and cysts?

DR. ARTHUR H. CURTIS, CHICAGO, ILL.—I do not employ the Pfannenstiel incision and therefore it is incumbent upon me to avoid bias in expressing my views. I have had occasion to open the abdomen subsequent to operation performed by others in many cases. In these I have been impressed with the deficiency of peritoneal and fascial tissues. This is so marked that closure of the peritoneum and fascia is exceedingly difficult, so much so that I always dread to operate on a patient who has previously had a Pfannenstiel incision. I should think that, with the necessary dissection of the abdominal wall, there would be a great tendency to infection between the layers, with the necessity of establishing secondary drainage in a rather considerable percentage of cases.

DR. W. A. COVENTRY, DULUTH, MINN.—When you want a nice clean non-visible abdominal scar in a young girl it is a fine incision to make because years after you cannot find the scar. I have never seen a keloid scar in a Pfannenstiel incision. You do get serum in the wound once in a while, and I have had one infection. The method of approach and exposure in my opinion is not so good as in a longitudinal incision.

DR. WILLIAM F. MENGERT, IOWA CITY, IOWA.—We have been using both of these incisions at the University of Iowa recently. Closure of an abdominal wound depends on two things: gentle handling of tissue and accurate approximation. The principal advantage of the Pfannenstiel incision is the ultimate cosmetic effect. The principal advantage of the Maylard or, as we have been calling it, the Bardenheuer incision, is excellent exposure, since it is made directly over the condition which the surgeon wishes to reach. Particularly have we found it of advantage in fat women with overhanging, pendulous folds, because the incision is made below the fold, in the upper portion of the mons veneris.

DR. HUNTER (closing).—Dr. Johnson's point that diastasis recti cannot be completely repaired with the Pfannenstiel incision is well taken. However, the rectus muscles can be approximated below the umbilicus.

I was aware through a personal communication of Dr. Heaney's objection that the pubis was anesthetic following this incision. I purposely questioned all patients whom I could contact and I failed to find any instance in which anesthesia occurred.

Dr. Waugh's point that the transversalis fascia is separated longitudinally is a valid one. I would stress that there is, however, in the Pfannenstiel incision absence of lateral tension caused by separation of the aponeurosis of the deep fascia. I do not mean to imply that incisional hernias do not occur with these incisions. I merely meant to say that they are diminished in the Pfannenstiel and Maylard incisions. One cannot base conclusions on impressions. One must make factual studies. The follow-up in these cases was made by examination, not by letter.

and continuously negative, or after three consecutive negatives if their throat cultures had been positive for hemolytic streptococci. No attempt was made to isolate the babies of mothers with the various forms of streptococcal infections on the basis of current pediatric belief that newborn babies are not susceptible to scarlet fever. The infants of uninfected mothers were isolated from those of known infected mothers by barrier technique.

From this time (January 17), all individuals who developed scarlet fever or other clinical manifestations of streptococcal infections could be traced definitely to the patients already mentioned. The maternity ward was reopened February 17, twenty days after appearance of the last definite infection, and three days after the removal of all remaining patients to the isolation ward.

#### CLINICAL DATA

Between Dec. 17, 1938 and Jan. 17, 1939, 179 adults and 147 newborn infants were admitted to the obstetric service. During the following month (to February 17), 7 adults and 63 babies were received. During this two months' period, 140 individuals entered the adjacent gynecologic wards. Sixty-six nurses, 34 medical students, 3 secretaries, 16 maids and food-handlers, and 20 staff members were exposed to one or more of the obstetric patients or attendants harboring beta-hemolytic streptococci (Table I). Bacteriologic study showed that 80 of the 675

TABLE I. THE DISTRIBUTION OF THE VARIOUS DISEASE ENTITIES IN THE DIFFERENT CLINICAL SUBJECTS

DISEASE	ANTE- PARTUM WOMEN	POST- PARTUM WOMEN	BABIES	DOCTORS AND NURSES	OTHERS
Asymptomatic carriers	1	11	4	9	9
Scarlet fever	1	10	0	2	1
Rhinitis	0	0	3	1	1
Sore throat	3	5	0	6	3
Tracheobronchitis	0	0	7	0	0
Lymphangitis	0	0	0	1	0
Endometritis	0	2			

individuals concerned harbored beta-hemolytic streptococci at some time during the epidemic; while 5 others had clinical but no bacteriologic evidence of infection. Among the former group there were 34 asymptomatic carriers, 14 cases of scarlet fever, 22 of upper respiratory infection, 2 of endometritis, 1 of lymphangitis, and 7 of tracheobronchitis in the newborn. Of the 5 patients not studied bacteriologically, 1 had scarlet fever, 3 upper respiratory infections, and 1 (newborn) tracheobronchitis. Eleven cases of scarlet fever occurred among the obstetric patients, of whom only 1 was undelivered. In addition there were 2 physicians (from the obstetric staff) and 1 secretary who developed scarlet fever. In spite of the fact that the nurses were undoubtedly exposed more than any other group, and 5 were carriers of the offending strain of streptococci, no cases of scarlet fever appeared, although a few developed pharyngitis. This may be attributed to the fact that they had been immunized by the Dick technique. The incubation period for the cases of scarlet fever was from two to five days, with an average of three days. The exposed babies, who showed evidence of infection, had an incubation period of from seven to fourteen days, with an average of eight days.

The diagnosis of scarlet fever was never made in the absence of rash, although it was felt that clinically those patients with severe upper respiratory infections differed only in the absence of cutaneous manifestations.

In the babies, the clinical picture was that of an initial upper respiratory infection, which in certain instances progressed within one to three days to a tracheobronchitis. The nasal and tracheal discharges became abundant and tenacious. The respirations were labored, the temperatures rose to 101° F. to 104° F., and a moderate cyanosis made its appearance. No baby presented a rash or desquamation. In all but three instances the babies showing severe infections were of mothers who had scarlet fever.

These individuals had attended Mrs. H. C. (1) during her delivery and were relieved from duty. One nurse had hemolytic streptococci in the throat; the other two were not cultured. Mrs. C. W. (8), who was delivered on December 26, was in contact with Mrs. W. (2) and Mrs. F. (4) in the labor room and later in the ward. These three women were delivered in the same room and were given gas anesthesia from the same machine. On Jan. 5, 1939, Mrs. C. W. (8) had a transient rash associated with mild upper respiratory symptoms which were concealed from the staff and revealed only after her return home. She was discharged on January 15, and five individuals in her family developed either scarlet fever or sore throat within one week after her arrival home. This patient (8) had been in the same post-partum ward with Mrs. F. (4), Mrs. W. (2), and Mrs. M. S. (9) and later with Mrs. V. M. (15). Mrs. W. (2), who earlier had a rhinitis, later developed scarlet fever with septicemia and was transferred to the isolation ward where she eventually made a good recovery. Mrs. F. (4) also contracted scarlet fever, with cervical adenitis, and was treated on the isolation ward. Mrs. M. S. (9), who was delivered January 9, acquired scarlet fever on January 12. Mrs. V. M. (15) developed scarlet fever eight days after delivery. Mrs. I. F. (10), who had no direct contact with any of the patients previously mentioned, presented a severe endometritis two days after delivery. Vaginal cultures were positive for beta-hemolytic streptococci, but throat cultures were negative. She had been delivered by a student (11), who was discovered later to be a carrier. On January 14, the resident (12) on the obstetric service developed scarlet fever following a prodromal pharyngitis. The next day the nurse (13), who cared for him, complained of a mild pharyngitis. On January 15, one of the departmental secretaries (14), who had taken dictation from the resident (12), had mild fever and sore throat. On the sixteenth, typical clinical scarlet fever appeared, and she was sent to the isolation ward where she developed right otitis media but made an uneventful recovery.

Previous to January 13, all suspected and proved cases of scarlet fever had been transferred to the isolation ward, but other precautionary measures were not strictly enforced. On this date all individuals having had contact with these patients were subjected to throat cultures, the report from which (January 14) revealed two carriers, a ward maid and the previously mentioned resident (12). On January 16, throat cultures were made on all patients and attendants; two nurses, one student, and ten patients were found to be asymptomatic carriers of beta-hemolytic streptococci with colony morphology typical of the scarlet fever strains.

The service was closed to new admissions on January 16, and on the following day the entire hospital was restricted to the acceptance of emergency cases, following the appearance of scarlet fever in one of the surgical residents (16) on January 15, leading to the fear that the disease might not have been localized. Two days later the same diagnosis was made on an office boy in the Children's Hospital, physically separated from the General Hospital. No cultures were made on the office boy but later serologic study showed the resident to be infected with the type of streptococcus isolated from the obstetric patients.

Precautionary measures adopted on January 16 included the exclusion of all visitors, the dismissal of medical students from ward duties, the wearing of masks and gowns by all individuals entering the ward, and the adoption of the usual strict isolation techniques. Moreover, the patients on obstetrics and gynecology were divided into three groups, which were treated as separate units: (1) those who had no known contact with infected individuals or carriers and whose throat cultures were negative; (2) the gynecologic patients who had been free from the disease and among whom no carriers had been detected; and (3) those who were infected or harbored the organisms in their throats, or who had been exposed to definite cases or carriers. All patients presenting clinical scarlet fever were removed with their babies to the isolation ward. Others in this group who did not show scarlet fever were subjected to room isolation. Nurses beginning or finishing their services on the ward were required to have two consecutive negative throat cultures before the change was made. All carriers were dismissed from duty and hospitalized or isolated in their homes. Delivered patients were discharged home as soon as possible after one negative throat culture if they had been previously

Two strains (one from an early scarlet fever patient and one from a case of pharyngitis) were sent to Dr. F. Griffith,\* of London, who designated them as Type 3 and Type 12, respectively, on the basis of agglutination tests with his type specific antisera.<sup>10</sup>

These strains were then used to produce antisera in rabbits for testing all of the other Group A strains by direct agglutination and agglutinin absorption techniques to determine those antigenically identical and thus presumably the same.

For this purpose, the serologic techniques of Dora Colebrook<sup>8</sup> were followed closely. Rabbits were immunized with heat-killed suspensions of the known Type 3 and Type 12 strains. Suspensions suitable for agglutination tests were prepared by formalizing the organisms obtained from a twenty-four-hour broth culture (150 c.c. of dextrose phosphate infusion broth). The cocci were then taken up in a small amount of M/15 disodium phosphate solution and transferred to a mortar where they were rubbed with a piece of absorbent cotton and additional phosphate solution. Repeated filtration until the suspension was uniform was carried out through cotton. This procedure was highly satisfactory in that only one of the 90 suspensions required remaking. This technique avoids the worst handicap of the serologic study of streptococci, spontaneous agglutination.<sup>†</sup>

The sera developed against the Type 3 and Type 12 organisms agglutinated the homologous organisms in 1:1600 dilution. For convenience, these will be spoken of as Type 3 and Type 12 sera, even though there was considerable cross reaction between the two. The 72 Group A strains were tested against the two sera by direct agglutination. The results are tabulated in Table III.

TABLE III. DIRECT AGGLUTINATION TESTS

TITER	TYPE 3 SERUM NUMBER OF STRAINS	TITER	TYPE 12 SERUM NUMBER OF STRAINS
0	5	0	5
1-100	0	1-100	0
1-200	0	1-200	11
1-400	0	1-400	26
1-800	6	1-800	13
1-1600	59	1-1600	15
Total	70		70

The most consistent findings were obtained with the Type 3 serum, but it was impossible to establish by this procedure the identity of all strains because of the cross reactions obtained with Type 12 serum.

Agglutinin absorption tests were performed on each of the 72 strains using the Type 3 serum. Similar antigenic content was indicated by exhaustion of the antibody content. Two-tenths cubic centimeter of 1:25 Type 3 serum was mixed with 0.2 c.c. of a suspension of the unknown organisms containing approximately 60 billion cells per cubic centimeter. The mixtures stood one-half hour at room temperature with occasional shaking, were then centrifuged, and 0.2 c.c. of the clear supernatant fluid pipetted off and tested for agglutinins by mixing with 0.2 c.c. of an agglutinating suspension of the Type 3 organism. Agglutination indicated antigenic dissimilarity between the homologous and unknown strains, because the latter had failed to exhaust the antibody content of the Type 3 sera in a dose three times the minimum absorbing dose of the known Type 3 strain. (This was previously determined to be 20 billion organisms per cubic centimeter.)

Sixty-four strains exhausted the 1:25 dilution of antibodies. Five of the remaining eight strains which did not remove the agglutinating antibodies had not been agglutinated in the direct tests. Two of the others later gave atypical sugar reactions, and one showed an atypical colony morphology.

\*The authors express their appreciation to Dr. F. Griffith, of London, for aiding us in the preliminary serologic survey.

†This is the first time as far as is known that this procedure has been reported for use with streptococci. The technique was described to us by Dr. W. M. Hale who obtained it from Dr. I. C. Kakavas of the University of Delaware, who has worked out the technique for use with tubercle bacilli.

There was no adult death in the series, but 2 babies died of tracheobronchitis with pneumonia. Among the adult patients there were 7 complications, including one of each of the following: superficial abscess of the finger, septicemia, generalized peritonitis, mastitis, otitis media, erysipelas, and superficial thrombophlebitis of the leg.

Asymptomatic carriers were treated with nasal instillations of 10 per cent argyrol, t.i.d. Prontylin was administered orally to a total dosage of from 140 to 1,080 gr., the largest daily dose being 80 gr. It was necessary to give at least 250 gr. within six days before the throat cultures became negative. In one instance the organisms disappeared from the throat only after the administration of 1,080 gr. over a twenty-two-day period. Since more than 50 per cent of these patients subsequently showed positive throat cultures, it is obvious that prontylin was of little value in controlling the carrier state. The acute infections were likewise treated with sulfanilamide and appeared to respond better. In these cases, larger doses, 120 gr. daily, were generally administered. The complications which arose were treated individually. Treatment of the babies was symptomatic.

Out of 19 case units (mother and baby) followed up directly or by correspondence after discharge from the hospital, 4 were known to have been the focus of an endemic outbreak of streptococcal infections. These patients had either had scarlet fever or upper respiratory infections or were known carriers. With the one exception previously noted, Mrs. C. W. (8), all of these patients had 3 negative throat cultures before discharge, or were accepted for control by the home physicians.

#### BACTERIOLOGIC DATA

From the recognition on Jan. 13, 1939, that an epidemic existed, until all precautionary measures were eliminated on April 2, 1939, 1,374 cultures for beta-hemolytic streptococci were taken. Eighty-nine individuals had one or more positive cultures as shown in Table II. Seventy-three of this group were actually in

TABLE II. SITES FROM WHICH BETA-HEMOLYTIC STREPTOCOCCI WERE OBTAINED IN 89 PATIENTS

AREA CULTURED	PATIENTS, DOCTORS, NURSES, MAIDS, ETC., ON SERVICE WHEN EPIDEMIC STARTED		NEW PATIENTS ADMITTED AFTER SERVICE REOPENED	
Throat alone	68	72* cultures	14	14 cultures
Throat and vagina	1	2		
Vagina alone	2	2	2	2
Throat and erysipelas	1	2		
Throat and hand infection	1	2		
Total	73	80 cultures	16	16 cultures

\*Four individuals had two different hemolytic streptococci in throat culture.

involved in the epidemic, while the remaining 16 were asymptomatic carriers admitted after the service had been reopened. The figures given do not include cultures taken from patients removed to the isolation ward.

Ninety-six strains of beta-hemolytic streptococci were obtained from these 89 individuals. One strain was lost and 95 were subjected to Lancefield grouping, Griffith typing, agglutination and agglutinin absorption, in order to determine which strains were identical with the Type 3 streptococcus isolated from the patients with scarlet fever, and also to chemical reactions, fibrinolysis tests, and erythrogenic toxin determinations.

Lancefield grouping tests were done according to the techniques outlined by Coffey.<sup>6,7</sup> All strains the acid extracts of which did not give precipitates with Group A antiserum obtained by immunizing rabbits with known Group A organisms were excluded after two negative tests. Scarlet fever strains of hemolytic streptococci are practically always of Group A. Among the 95 tested strains, 82 reacted with the Group A sera, but the 10 which had been isolated after the epidemic proper were excluded from further serologic study, thus leaving 72 for consideration.

The four Type 12 strains, which were definitely identified, were isolated from one patient with simple pharyngitis and three asymptomatic carriers and appeared to have no direct bearing upon the development of the epidemic.

Thirty-two samples of air, each representing 10 cubic feet, were taken by Dr. K. MacDonald from several locations on the maternity ward during the height of the epidemic. In the entire number of samples, which represented a total of 320 cubic feet of air, only 4 colonies of hemolytic streptococci were grown. Under normal conditions of respiration, a man breathes approximately this amount of air in twenty-four hours. The extreme dilution of streptococcal droplet nuclei thus demonstrated, suggests that the danger of air-borne transmission must have been very slight.

#### DISCUSSION

According to Burton and Weir (1936) scarlet fever during pregnancy and the puerperium was first described by Hamilton, in 1470, with later accounts by Welsh (1635) and Ludwig (1758). In 1799, Mafatti, and, in 1826, Senn presented their classical reports, followed in 1876 by Olshausen's dissertation. The most recent authoritative article is by Sèdallian (1935), which also includes observations on the newborn. Byers, in 1912, recorded an epidemic in Belfast with approximately 1,500 cases, representing 1.8 per 1,000 of the population. During 1910 and 1911, 1,259 cases of scarlet fever were treated in the city hospitals, which during the same year cared for 2,964 obstetric patients, none of whom contracted the disease.

It has long been recognized that the incidence of scarlet fever is much greater in puerperal than in pregnant women, and, in 1876, Olshausen postulated an increased immunity during gestation. This view has been widely accepted and is supported by collected statistics, which indicate a puerperal mortality rate has varied from 0.0 to 100.0 per cent and the infant mortality up to 13 per cent.

During the 13 years from July 1, 1926, to June 30, 1939, there were approximately 12,000 deliveries in the University Hospital, with 13 cases of scarlet fever, 2 ante partum, and 11 post partum. Eleven of these patients were observed during the epidemic here recorded, with one case each in 1935 and 1936. The single fatality (1936) involved a primigravida, aged 22 years, who delivered spontaneously thirteen days after the onset of the disease and died forty-nine days post partum from parametritis and streptococcal septicemia.

In the present epidemic, the incidence of clinical scarlet fever was 1:140 in ante-partum women, 1:14 in those who were delivered, and 1:83 among the attendants. In the State of Iowa, there were 1,526 reported cases of scarlet fever during the three months (December, 1938, through February, 1939), an incidence of 1:1,650 of the population. In the opinion of the state epidemiologist the reporting of scarlet fever is so inadequate that the actual incidence is considerably greater than indicated.

It is generally believed that newborn children are immune to the disease, a view which is supported by Rominger (1919), Dorner (1920), and Bohn (1877). On the other hand, Boxall (1888) stated that the child might contract the disease in mild form if allowed to suckle the mother, and Allan (1905) recorded scarlet fever in a child 3 weeks old.

Among the 64 strains, however, was the Type 12 organism which almost exhausted the Type 3 serum in the 1:25 dilution, and thus prevented the definite separation of the Type 3 and Type 12 strains.

To attack the differentiation from the other angle, undiluted Type 12 serum (3 c.c.) was absorbed with five fractional doses of the centrifuged and washed Type 3 cells from a liter and a half of broth culture. After this treatment the serum no longer agglutinated the Type 3 organism in a titer of 1:10 but still agglutinated the Type 12 homologous strain in a titer of 1:320. This serum was specific for the Type 12 organisms in the collection and was used in a strength of 1:5 (final dilution 1:10) to test each of the other 71 strains. The three strains which were agglutinated and were therefore designated as Type 12, had been among those agglutinated in the highest dilution in the direct agglutination tests with the unabsorbed Type 12 serum.

Finally, undiluted Type 3 serum was absorbed with Type 12 organisms in a similar manner and as a result no longer agglutinated the Type 12 strain in a dilution of 1:12 but caused clumping of the homologous organisms to a titer of 1:96. There was, therefore, a demonstrable antigenic difference between the two, although the Type 12 organism could practically exhaust the Type 3 serum in a 1:25 dilution.

The final results of this part of the study are recorded in Table IV.

TABLE IV. TYPE DISTRIBUTION AMONG 72 GROUP A STREPTOCOCCI ISOLATED FROM INDIVIDUALS INVOLVED IN THE EPIDEMIC

	TYPE 3	TYPE 12	OTHERS
Patients			
Adult	32	3	4
Babies	11		
Doctors	4		2
Nurses	5	1	1
Maids	4		
Medical students	3		1
Secretary	1		
Total	60	4	8

*Biochemical Reactions.*—As noted above, 64 of the strains were found to be Type 3 or Type 12. Two of these were lost but the remaining 62 were subjected to biochemical tests (Coffey<sup>6,7</sup>) and found not to hydrolyze sodium hippurate or ferment sorbitol but did ferment lactose, trehalose and salicin, and consequently can be classified as *Streptococcus pyogenes*.

Generally the ability of the organisms to dissolve human fibrin was poor; in 75 per cent there was no fibrinolysis under the Tillett technique,<sup>14</sup> whereas a strain unrelated to the epidemic caused lysis in thirty minutes, indicating that the plasma used was susceptible. The lack of strong fibrinolytic activity is consistent with the relatively mild clinical course of the scarlet fever and of the other related infections. The results are tabulated in Table V.

On the other hand, the demonstrable amount of erythrogenic toxin was of the usual order, since a 1:1000 dilution of a broth culture in a dose of 0.1 c.c. gave a reaction comparable to that of one skin dose of Dick toxin.

TABLE V. RESULTS OF FIBRINOLYTIC TESTS IN 62 GROUP A STREPTOCOCCI

RAPIDITY	TYPE 3	TYPE 12
4-plus	0	0
3-plus	2	0
2-plus	7	2
1-plus	4	1
Negative	45	1
Total	58	4



and gave feedings during the night was overlooked because she was off duty at the time the cultures were taken from the night staff, but after both babies had developed evidences of infection (one died from pneumonia and septicemia) her throat culture showed beta-hemolytic streptococci. In another instance, an infected baby was responsible for the development of a carrier condition in a nurse, who had previously been negative. The nurse aspirated mucus from the throat of the baby during the terminal tracheobronchitis and then inserted her fingers in her mouth. Two days later throat cultures revealed streptococci (Type 3), but she had no clinical manifestations and became negative after treatment.

The clinical reaction to infection with any organism, including the beta-hemolytic streptococcus, depends upon the susceptibility of the host, the pathogenicity of the invading organisms, and the number of organisms attacking the host. Variations in these factors determine whether individuals repeatedly exposed during an epidemic will develop the disease, become asymptomatic carriers, or remain uninfected. Among the 84 individuals directly and repeatedly exposed, approximately 57 per cent developed some manifestation of a streptococcus infection or became carriers, while the remaining group did not acquire the infection as shown by repeated negative throat cultures and the absence of clinical symptoms.

Evidently newborn babies are somewhat more resistant to invasion by beta-hemolytic streptococci than are adults, but this immunity disappears within eight to fourteen days. Of the 33 babies directly exposed, 14 harbored the streptococci. Except in one instance, the babies of mothers who developed clinical scarlet fever showed severe upper respiratory infections. Three additional babies had mild rhinitides and four became asymptomatic carriers. The remaining infants showed no bacteriologic or clinical evidence of invasion by the streptococci. These experiences suggest that the supposed immunity of newborn children to the beta-hemolytic streptococcus has been greatly exaggerated.

#### SUMMARY AND CONCLUSIONS

Clinical and bacteriologic studies of an epidemic of scarlet fever and associated beta-hemolytic streptococcal infections were made during an epidemic on the obstetric wards of a general hospital. The epidemic evidently had its origin from a patient admitted with a severe upper respiratory infection acquired during an unreported contact with a relative in the prodromal stage of scarlet fever. From this focus the disease apparently spread by direct contact, and the situation was finally controlled by the adoption of strict isolation techniques.

The 675 individuals subjected to greater or lesser exposure included 210 newborn children and 465 adults. Fourteen of the infants showed upper respiratory infection; 7 of these progressed to severe tracheobronchitis, but there were no cases of scarlet fever. Among the 66 adults who harbored the streptococci, 14 had typical scarlet fever, 2 showed puerperal endometritis, 13 had pharyngitis, 5 developed rhi-

In the epidemic here recorded, no effort was made to isolate the babies from the mothers, even when there was clinical or bacteriologic evidence of streptococcic infection. A total of 210 babies were more or less exposed during the epidemic. In 177 instances direct exposure was not proved and none of these babies developed any manifestations of infection, while 33 infants had known direct contacts with infected adults, and 10 (30.3 per cent) gave objective evidence of infection. There was no clinical scarlet fever. Respiratory symptoms appeared eight to twenty-six days after birth in the breast-fed babies. The only two fatalities occurred in premature infants who had never been suckled, but who were fed by a nursery maid who was found later to be a carrier. The mortality rate for those known to have been exposed was 6.1 per cent.

Watson (1928), in reporting an outbreak of puerperal sepsis in the Sloane Hospital for Women, emphasized the role of asymptomatic carriers in the spread of the streptococci, and pointed out that carriers are not uncommon. It is also well recognized that the beta-hemolytic streptococcus may produce a variety of clinical manifestations, depending upon the site of the infection. The two cases of severe endometritis in this series were most probably due to the scarlet fever streptococcus, since this organism was isolated from the uterine discharges. One of these patients had streptococci in the throat while the other was attended by a medical student who was shown later to be a carrier. In the two women with skin infections (localized superficial abscess and erysipelas), throat cultures revealed organisms identical with those grown from the local lesions. The 14 cases of scarlet fever were probably acquired through droplet infection from others with the disease or in its prodromal stage, or from asymptomatic carriers, although the exact mode of transfer was not always clear in view of the obvious multiple exposures early in the epidemic. The best instance of transfer by a carrier involved a ward maid whose duties included the distribution of food and fluids to the post-partum patients. She was dismissed from duty as soon as the carrier state was recognized, but six days later after a single negative throat culture she returned to care for nine ante-partum patients. Five days later one woman in this group developed scarlet fever and another presented a throat culture positive for beta-hemolytic streptococci; cultures taken from the maid at the same time were again positive. All three organisms (from the maid and the two patients) were later shown to be the same. After her return to duty, the maid was required to wear a gauze mask, but it is apparent that this did not offer adequate protection to those in contact with her. It is also obvious that the single negative culture was given undue significance.

In all but two of the babies, the infection was evidently acquired from the mother during the nursing periods, but in the two exceptions, a carrier was probably responsible. In both instances the babies, which were small, were isolated in the premature nursery and had no contacts except with the attendants. The nurse-maid who prepared

## THE TREATMENT OF BACTERIEMIAS WITH SULFANILAMIDE\*

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THE treatment of puerperal bacteriemia has been, until recently, an almost unsurmountable problem. The lack of a universal bacteriologic and pathologic nomenclature has retarded fruitful discussions concerning morbidity, mortality, and end results from various forms of therapy.

For the past ten years the Department of Obstetrics, University of Tennessee, has been interested in accumulating such information as would serve as a basis for future bacteriologic and pathologic classifications as well as for standard therapy of puerperal infections. With particular reference to patients having positive blood cultures, I have analyzed these findings to date; but since this group of patients was entirely too small to formulate any foundation for permanent guidance, it was decided that if similar studies from other institutions could be obtained much could be gained by comparative study.

Eighty-one questionnaires were sent out to institutions accredited by The American Board of Obstetrics and Gynecology for the training of interns and residents. Questions submitted were:

1. Outline of bacteriologic nomenclature.
2. Outline of pathologic nomenclature with special reference to definition of terms: septicemia and bacteriemia.
3. Total number of patients having positive blood stream infections during 1927 to 1937 inclusive, with organisms isolated.
4. A brief outline of therapy used in above cases with end results obtained with each type of therapy, and if possible, grouped by years with therapy above cases.
5. End results of all cases grouped. A. Before sulfanilamide therapy; and B. during sulfanilamide therapy.

Thirty-three such institutions replied, but only five were able to answer the full questionnaire. Quite a large number apologized for not having sufficient time to analyze their cases of patients having positive blood infections from 1927 to 1937.

It was evident from the return questionnaires that there were no uniform bacteriologic nomenclature, at least with particular reference to the streptococcus group. All more or less conformed to Lansfield's classification.

The bacteriologic classification used in our department was suggested by the Department of Bacteriology, University of Tennessee.

\*Read at the Eleventh Annual Meeting of the Central Association of Obstetricians and Gynecologists, Kansas City, Mo., November 2 to 4, 1939.

nitis, while the remaining 32 were asymptomatic carriers. Seven of the adult patients and two of the newborn infants developed various complications. There was no adult fatality, but two babies died from pneumonia following tracheobronchitis.

In general, this epidemic confirmed the general belief that the puerperal woman is more susceptible to scarlet fever and to other manifestations of beta-hemolytic streptococcal infections than is the antepartum individual. On the other hand, the common belief that the newborn child is immune to these organisms was not substantiated.

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#### DISCUSSION

DR. FRED L. ADAIR, CHICAGO, ILL.—It is a well-known fact that one attack of scarlet fever seems to protect actually or relatively against a subsequent attack of this disease. This brings up the question of whether an attack of scarlet fever might protect against other types of streptococcal infection. Some years ago a study was carried out in which we found that women who had had scarlet fever were less susceptible to puerperal infection than those who had not had scarlet fever.

It also brings up the question of whether the pregnant woman with scarlet fever transmits the infection to the newborn child. So far as we have been able to find, there are no cases in the literature where the streptococcus has been found in the fetus born of a mother who had scarlet fever during pregnancy. Cases are reported where the newborn baby had a rash. There are two possible explanations: one is that the fetus actually had a streptococcal infection, and second, that the fetus may have erythrogenic toxins which produced a rash without having an actual infection.

It is hardly fair to conclude that because a woman or child has an infection with beta hemolytic streptococcus it is scarlet fever, and she is going to develop a rash. The rash may be due to one or two factors. The organism may have unusual capacity to produce erythrogenic toxins which account for the rash, or the host of the streptococcus may have a peculiar susceptibility in the way of an allergic reaction which may account for the development of a rash in that particular person. The main thing to consider is that we are dealing with streptococcal infection, and its clinical manifestations in the presence or absence of a rash are not so important.

I think one might conclude from Dr. Plass' observations that the newborn infant is susceptible to streptococcal infection but is not too prone to develop erythrogenic symptoms. In other words, the skin reaction of the newborn baby to beta hemolytic streptococcus is somewhat different from that of the adult.

DR. PLASS (closing).—The clinical problem involved in carriers is to detect them. It is obviously impossible in a large service to culture the throat of every woman and yet we know that from 5 to 10 per cent of the population may harbor beta hemolytic streptococcus. I believe that the laissez-faire attitude which we have always adopted is about all we can do.

It was apparent from the study of organisms isolated from both groups that hemolytic streptococci accounted for the largest number of patients infected. In both groups, the hemolytic streptococcus accounted for 74 out of the total of 138 cases of 53.6 per cent studied. Therefore, the hemolytic streptococcus accepted by the profession, as having been introduced from without, is still the problem to overcome.

In general, the replies to the pathologic nomenclature conformed to the one used in our department: i.e., (1) endometritis, (2) parametritis, and (3) peritonitis. But blood stream invasion, termed septicemia or bacteriemia, was not in harmony.

The definition for septicemia and bacteriemia, returned through these questionnaires, varied anywhere from saying, "The condition is the same and the terms are interchangeable" to complete omission of these terms and in their place the adoption of "puerperal infection." Several stated, "A bacteriemia indicates a mild type of infection with a transient passing of organisms into the blood stream with no other evidence of infection"; others note, "Septicemia indicates a definite source of infection in local or remote parts of the body with or without positive blood cultures."

Unless positive evidence is presented to substantiate the real pathology, such differences in opinion preclude any possibility for unity of thought. Our department has abandoned the term septicemia, and designates all patients having positive blood stream infections as a case of bacteriemia. We feel that more patients will show positive blood cultures if close attention is devoted by the clinician to the proper time of taking blood cultures and if a more diligent search is made by the bacteriologist.

It is thought that the period of gestation and the method of termination might have some bearing on the number of bacteremias.

TABLE III. BACTERIOLOGIC CLASSIFICATION WITH RELATION TO PREGNANCY TERMINATION

	TERM		ABORTION		UNDELIVERED		TOTAL
	OPER.	SPONT.	IND.	SPONT.	PNEUMONIA	PYELITIS	
Hemolytic streptococcus	5	13	9	7	0	0	34
<i>B. welchii</i>	6	2	0	1	0	0	9
Pneumococcus	0	1	1	1	2	0	5
Staphylococcus	2	1	0	0	0	0	3
<i>B. coli</i>	1	1	0	0	0	1	3
Nonhemolytic streptococcus	0	1	0	1	0	0	2
Influenza	0	1	0	0	0	0	1
Total	14	20	10	10	2	1	57
	34		20		3		

To our surprise, the streptococcus was found present in more spontaneous deliveries than in those by operative interferences. Moreover, there was only a negligible difference in the numbers of infections resulting from criminal or spontaneous abortion. However, the Welch's bacillus was found, most often in operative cases.

TABLE I. BACTERIOLOGIC CLASSIFICATION OF UNIVERSITY OF TENNESSEE

*Usual Organisms Found in Puerperal Infection*

## 1. Streptococcus:

## Alpha viridans

(a) Human organisms—pathogenic to man, 30 subgroups

## Beta (Hemo.)

(b) Mastitis in cows

(c) Pathogenic to lower animals

(d) Cheese

(e) Milk

(f) Causes purulent respiratory infection in man

(g, h, k) Not pathogenic to man

*Gamma, nonhemo., anaerobic organisms*

## 2. Staphylococcus hemolytic and nonhemolytic

3. *B. welchii*4. *B. coli*

## 5. Gonococcus

## 6. Pneumococcus

7. *B. diphtheria**Organisms Found in Our Series 1927-1937*

Hemolytic streptococcus	34 cases
<i>B. welchii</i>	9 cases
Pneumococcus	5 cases
Staphylococcus	3 cases
<i>B. coli</i>	3 cases
Nonhemolytic strep. (anerobic)	2 cases
Influenza	1 case
Total	57 cases

This analysis reveals that the hemolytic streptococcus was found in 34 of 57 cases, or 69.5 per cent. The nonhemolytic type occurred in only 2 cases.

Total blood cultures compiled from all questionnaires are grouped to compare with our series.

TABLE II. COMPARATIVE STUDY OF ORGANISMS FROM OTHER INSTITUTIONS 1927-1937

	J. ROSENHEIM BROOKLYN	E. D. PLASS U. OF IOWA	N. MILLER U. OF MICH.	MC NEILE U. OF S. CALIF.	H. F. BECKMAN U. OF IND.	TOTAL
Streptococcus	4	8	6	19	3	40
<i>B. welchii</i>				3		3
Pneumococcus				4		4
Staphylococcus	3	1	2	5	3	14
<i>B. coli</i>	2	1	1	2		6
Nonhemolytic strep.	2	2	1	1	3	9
<i>Staph. viridans</i>	1	1	1	1		4
Paratyphoid			1			1
Total	12	13	12	35	9	81

The hemolytic streptococcus was approximately in the same proportions as in our series. It occurred in 40 out of 81 cases, or 49.3 per cent. The nonhemolytic streptococcus occurred in 9 cases. The remaining number in either series did not suggest any significance for comparative study.

of cells and hemoglobin content. Moreover, it is necessary to have large quantities of blood available in the form of a "blood bank."

CASE 2.—A colored female, aged 34 years, para vii, gravida viii, was admitted to the hospital on May 10, 1939, with the history of having passed one quart of blood, four days before admission. This painless bleeding was later associated with lower abdominal pains, passage of clots, and dizziness. When bleeding reoccurred several days later, a private physician was called who did a vaginal examination. This was followed by profuse bleeding, and the patient was immediately sent into our service. Physical examination revealed the patient in mild shock with blood pressure 90/70, red blood count 2,390,000, hemoglobin 9.75 Gm., temperature 102° F., and the pulse 100. A vaginal examination of this full-term gravid patient revealed a placenta previa which had been perforated before admission to hospital. There was a foul vaginal discharge. Since no bleeding was present, it was decided to combat infection by large doses of sulfanilamide and blood transfusions. An intraovular bag was inserted through a 5 cm. dilated cervix after thirty-six hours of above treatment. The bag was expelled, and a dead, maccrated fetus was delivered by version and extraction. The subsequent course of the disease was one of severe sepsis. The 14 blood cultures taken were always positive except for the one taken before and immediately following delivery. Multiple lung abscesses developed in spite of the heroic therapy of 886 gr. of sulfanilamide and 25 transfusions, totaling 12,500 cm. of blood. Patient died on the sixty-eighth day of her illness (July 18, 1939). Table IV outlines the abstracted case.

TABLE IV

NO. DAYS	RED CELLS AV.	Hb AV. GM.	SULFANILAMIDE			CULTURE	METHEMO- GLOBIN	BLOOD GIVEN CM.
			AV. GR. DAILY	TOTAL GR.	BLOOD CON- TENT			
Predelivery								
1½	2,755,000	9.0	93	140	3.0	Neg.		T. 2,100
Postdelivery								
6	2,473,000	9.0	51	448	4.5 6th day 11.2	Pos.	37% sixth day 4 plus cyano- sis methylene blue started	Av.* 341 T. 2,150 Gt 4,250
4	2,150,000	8.2	60	668	4.5		Under methy- lene blue fell to 20% with abatement of cyanosis	Av. 225 T. 900 Gt 5,150
3	1,750,000	5.5	60	868	4.0	Pos.		Av. 666 T. 2,000 Gt 7,150
3	2,660,000	9.0	0	868		Pos.		Av. 750 T. 2,350 Gt 9,500
4	3,420,000	13.0	0	868		Pos.		Av. 450 T. 1,800 Gt 11,300

\*Av., average; T., total; Gt, grand total.

A small group of patients will develop rapid anemia that will necessitate repeated blood transfusions. This within itself is not a contraindication to the continuance with the drug. The development of cyanosis, resulting from methemoglobinemia and occasionally from sulfhemoglobinemia, should be constantly watched. The estimation of methemoglobinemia should be estimated if cyanosis develops.

I would not attempt to sponsor such reasonings as this analysis reflects; for it is generally accepted that the hemolytic streptococcus is nearly always introduced from without.

The general trend of therapy from all questionnaires conformed with us by giving general supportive measures, occasionally serum; but all stressed repeated blood transfusions. Sulfanilamide was used in such a small group of cases that no comparison of the end results with this drug could be analyzed. Some suggested that its use has lessened the number of positive blood stream infections; while others having had no experience, thought its use would prove of great value.

In our patients the administration of sulfanilamide has proved most advantageous. In the beginning, this drug was rather indiscriminately used in all of the more severe types of infections. Continued observation and study revealed that it would be given only in those cases presenting severe sepsis or positive blood cultures, and this, under constant surveillance. Moreover, its early administration inhibits obtaining the organisms causing the infection. The initial dose is usually fairly large, ranging from 80 to 120 gr. This massive dose serves to raise the blood sulfanilamide content to about 10 mg. in the first four hours. Subsequent doses range anywhere from 20 to 40 gr., four times a day for the first three days, and then are administered in accordance with the reduction of temperature and the amelioration of symptoms. Experience has demonstrated that this drug may act as a two-edged sword; while proving beneficial in most cases, it has produced death.

CASE 1.—(13298.) A colored female, aged 31 years, para ii, gravida iii, at full term, was admitted to the hospital on Dec. 30, 1938, apparently in early labor. A bag was inserted after thirteen hours of labor because of fetal distress. After eighteen hours the bag was expelled, and a normal delivery followed. The patient was immediately placed on sulfanilamide because of a post-partum rise of temperature of 102° F. with a pulse of 120. Red blood count was 4,050,000 with a Hb. of 9 Gm. The abdomen was tender over the uterus and there was a foul lochia. After six days, the patient gradually became semistuporous. The temperature had risen to 101° F. with a pulse rate of 120. The respiratory rate was labored and had increased to about 30 with occasional attacks of hiccoughs. Marked cyanosis was present. A daily dose of 120 gr. of sulfanilamide had been given and a total of 720 gr. was received without a check on blood sulfanilamide. The red blood count had dropped to 3,750,000, the hemoglobin content was 11 Gm., and the blood sulfanilamide 11 mg. Because of the apparent intoxication and susceptibility to sulfanilamide, the drug was discontinued. Despite this removal, the methemoglobinemia continued to rise and within a few hours was 27 per cent. Methylene blue was administered to offset the accumulation but failed when the methemoglobinemia rose to 42 per cent within forty-eight hours. The patient died on the eighth day of her illness, Jan. 8, 1939. Dr. Wendel had no explanation for this increased rise in the methemoglobin after the discontinuance of sulfanilamide.

The estimation of the blood sulfanilamide content level should have daily observations made, for quite often in some cases small dosage with less toxic symptoms will bring desired results, while in others the blood sulfanilamide content remains exceedingly low and not the sufficient level to overcome the infection, but only causing destruction



TABLE V. COMPARATIVE STUDY OF END RESULTS OF BACTERIEMIA 1927 TO 1937

	TOTAL CASES	CURED	DIED	PERCENTAGE DIED
Rosenheim Brooklyn	12	5	7	53.3
E. D. Plass U. of Iowa	13	6	7	55.5
N. Miller U. of Mich.	12	0	12	100
McNeile U. of S. Calif.	35	5	30	85.7
Beckman U. of Ind.	9	5	4	44.4
Totals	81	21	60	74.1

TABLE VI. END RESULTS IN BACTERIEMIA 1927 TO 1937

YEAR	MEDICATION	TOTAL CASES	CURED	DIED	PERCENTAGE DIED
1929	Blood trans. metaphen	1	0	1	100
1930	Blood trans. perf. serum	1	0	1	100
1927	Anti-strep. serum	4	1	3	75
1928	Anti-strep. serum and blood	7	2	5	71.4
1931-					
1935	Blood trans. and medical treatment	11	5	6	54.5
1930	Medical therapy	13	9	4	30.7
1930	Perfringes serum	3	3	0	0
1936	Blood trans. and sulfanil.	6	4	2	33.3
1937	Sulfanilamide	5	5	0	0
Totals		54	30	24	44.4

TABLE VII. COMPARATIVE STUDY

	YEARS	CASES	DEATHS	PER- CENTAGE
Pre-sulfanilamide				
Colebrook	1932-1935	82	55	70.7
Reinberger	1927-1935	43	22	51.1
Sulfanilamide-prontosil, etc.				
Colebrook	1936-1937	22	6	27.3
Reinberger	1936-1937	11	2*	18.1

\*Both patients admitted in moribund state, and inadequate treatment was administered -10 and -20 gr., respectively.

Likewise a comparative study (Table VII) was made of our series with that of Colebrook's of England.

The mortality for the entire 57 patients, including those treated by sulfanilamide, was 44.4 per cent. Excluding those treated by sulfanilamide, the mortality was 51.1 per cent. The mortality following the use of sulfanilamide was reduced to 18.1 per cent. Colebrook's figures in the pre-sulfanilamide group had a mortality of 70.7 per cent; our series, a mortality of 51.1 per cent. Colebrook's patients treated with sulfanilamide had a mortality of 27.3 per cent; ours 18.1 per cent. A review of the two deaths in our small series of 11 cases revealed inadequate treatment; for only 10 and 20 gr. were given, respectively. It is almost unbelievable that such immediate results were achieved with this comparatively new drug.

Since the beginning of the use of this drug our department of Obstetrics has been fortunate in having Dr. William B. Wendel, Department of Chemistry, University of Tennessee, in constant consultation.

Dr. Wendel has recorded much research relative to the action of this drug prior to its more general use. He advocated the intravenous administration of methylene blue to overcome methemoglobinemia. This procedure has permitted us to continue sulfanilamide therapy in the face of this apparent complication. It clears the cyanosis almost immediately. Within only a few days, the blood stream is rid of the infection, and except for the remaining mildly toxic symptoms, the patient is well in a few days. The administration of this drug bids fair as an adjunct in the treatment of general peritonitis. Our experience has been limited. But one such case indicates its bacteriostatic as well as its bactericidal effect until drainage could be established through a cul-de-sac puncture.

CASE 3.—(1367.) A white female, aged 25 years, para i, gravida ii, was admitted to the hospital on Aug. 20, 1939, with the history of having missed two periods. She had passed a catheter, about six days prior to her admission to the hospital. Following this instrumentation, large clots continued until admission to the hospital. The patient was acutely ill with a temperature of 101.6° F. and a pulse of 90. The entire abdomen was very tender and markedly rigid, with signs of general peritonitis. Vaginal examination revealed bleeding and a uterus the size of a two and one-half months' pregnancy. The red blood count was 7,750,000 with hemoglobin 13 Gm.; urine negative. During the first ten days, the patient ran a septic fever between 101° and 103° F., with three chills, pulse around 140, generalized abdominal pain, and rigidity and tenderness with localization in the pelvis. Treatment consisted of 620 gr. of sulfanilamide with a reduction in the red count down to 1,750,000 and hemoglobin of 7.5 Gm. On the fifth day in spite of two blood transfusions, the patient developed a methemoglobinemia, with a blood methemoglobinemia of 22 per cent and four-plus cyanosis. Both subsided after intravenous methylene blue. A pelvic abscess was drained on the tenth day. For the next twenty-one days the patient's temperature varied from 99 to 100° F., and the pulse 90. More than 500 gr. of sulfanilamide were given. Blood transfusions and supportive treatment increased the red blood count to 3,400,000 and hemoglobin to 9 Gm. During the next twelve days the patient ran a fever from 98 to 103° F. with a daily average rise of 102 to 103° F. At this period no sulfanilamide was given. Increasing pain and tenderness developed in the lower abdomen. This showed that the abscess had reoccurred and was drained through the cul-de-sac. Recovery was rapid and uneventful.

Because of the limited use of this drug, the question relative to grouping the cases into pre-sulfanilamide therapy could not be compared. In fact, none of the patients, in the reported group of compiled cases from questionnaires, had received any sulfanilamide.

This study (Table V) demonstrates the continued high death rate, for there were 60 deaths in 81 cases, or a mortality of 74.7 per cent, against 51.1 per cent for our own series treated prior to introduction of sulfanilamide.

Our own results in a comparative tabulation reveal a general improvement in mortality figures, even before the introduction of sulfanilamide, and a striking improvement after its use (Table VI).

neuritis, and exfoliative dermatitis that have proved to be very serious complications. A very sobering and insistent question continually obtrudes itself in the consideration of sulfanilamide therapy and that is: What permanent pathology is likely to follow from a drug which can cause such immediate signs of serious damage? Sulfanilamide therapy should have the backing of adequate consultation and the consent of the family.

DR. H. CLOSE HESSELTINE, CHICAGO, ILL.—Colebrook's study, which is probably the largest single one yet published, indicates that the value of this drug is a very limited one. Its value in hemolytic streptococcic infection is established. It seems worthy of trial as well in *B. welchii* infection. At the Chicago Lying-in Hospital our figures indicate that the anaerobic bacillus is unyielding to sulfanilamide. It is neither sane nor judicious to use sulfanilamide indiscriminately. Mortality and morbidity are potential dangers from this therapy. Perhaps residual damage is more common than supposed.

DR. GEORGE KAMPERMAN, DETROIT, MICH.—We have seen cases where we thought that the giving of sulfanilamide in itself caused a continuation of the temperature. We have had a few cases where results were not being obtained and sulfanilamide was stopped. Immediately after that the temperature dropped.

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## GRANULOMA INGUINALE (GRANULOMA VENEREUM) OF THE CERVIX\*

### AN ANALYSIS OF THIRTY-EIGHT CASES

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**I**N THE two-year period ending July 1, 1939, we have been able, by the utilization of various histologic techniques and staining methods, to demonstrate the specific histopathology of granuloma inguinale in 21 patients with granulomatous lesions of the cervix. Our success in these cases stimulated us to review the sections in all cases of cervical granuloma which had occurred at Charity Hospital of Louisiana during the preceding eight years, and as a result of this attempt it was possible to identify characteristic Donovan bodies in 17 additional cases.

We do not believe, however, that an incidence of 38 cases over a ten-year period by any means represents the true incidence of granuloma inguinale of the cervix in this institution. More serious attempts at diagnosis would undoubtedly have revealed a far greater number of cases. We are convinced that many large, exuberant cervical lesions, which simulate cancer in appearance but are never confirmed as such, are really granuloma inguinale. These lesions have remained undiagnosed in the past because adequate diagnostic methods were not employed, and they will continue to be undiagnosed in the future if such methods are not fully utilized.

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## SUMMARY

1. Puerperal bacteremia is more common than generally recognized.
2. During the period of this study 1927 to 1937, 15,000 patients were delivered.
3. There were 54 patients with positive blood stream infection, an average of 3.5 per cent per 1,000.
4. Hemolytic streptococcus accounted for 34 out of 54 organisms isolated.
5. There were 24 deaths out of 54 cases, mortality 44.4 per cent.
6. This study indicates that there has been a gradual, if not actual, reduction in ratio for type of therapy.
7. Sulfanilamide alone or with transfusion seemed to offer a sense of security, which otherwise has been absent; in that among the last 9 patients treated with this drug, there were no deaths.

## CONCLUSIONS

1. The high death rate from puerperal bacteremia, despite the advancement of scientific medicine, indicates that there is considerable room for improvement.
2. A clearer conception of the bacteriology and pathology will aid materially; however, more can be accomplished by prophylactic measures.
3. The avenues of invasion and multiplicity of the sources of infection in the parturient canal by the hemolytic streptococcus must be recognized.
4. Blood transfusion and sulfanilamide bids fare to out-distance any remedies heretofore applied.

## DISCUSSION

DR. R. T. LAVAKE, MINNEAPOLIS, MINN.—To aid in the preparation for this discussion, Dr. James F. Shandorf went over all cases of clinical sepsis treated with sulfanilamide since the first of the year at the University Hospital. There were 57 cases in all, including 42 septic abortions and 15 cases of clinical post-partum sepsis. All recovered but two. All of these also received as many transfusions as were deemed indicated. In only two of these did the cultures return positive for *Streptococcus hemolyticus*, namely, in two cases of abortion, which ended fatally. One of these patients was brought in practically moribund and died five hours after admission; and the other died on the fourteenth day.

Our immediate use of sulfanilamide therapy upon a clinical diagnosis of sepsis, is only a trial, in the endeavor to get the full bacteriostatic action of the drug as early as possible in case a *Streptococcus hemolyticus* is later identified by culture. Whether or not we will continue to feel justified in beginning sulfanilamide therapy before actually obtaining positive cultures of *Streptococcus hemolyticus* will depend upon further experience.

In none of our cases did a toxic reaction demand withdrawal of the drug. This is not, however, in accord with the general experience at the University Hospital. Here the drug had on various occasions to be withdrawn for the following indications: delirium and psychosis, 5 times; toxic fever, 4 times; acute hemolytic anemia, 11 times; jaundice and signs of severe hepatitis in urine and blood, 20 times. Most of these toxic manifestations cleared up under immediate withdrawal of the drug, forced fluids, and blood transfusions when indicated. From our immediate colleagues, we have also had reports of toxic agranulocytosis, peripheral

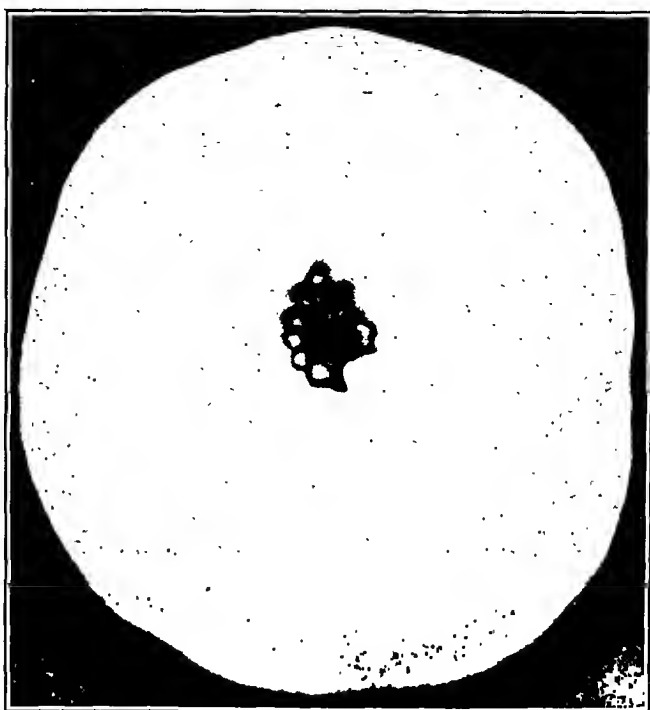


Fig. 1.—Early granuloma inguinale of the cervix. Note the close resemblance of the lesion to a cervical erosion.



Fig. 2.—Advanced granuloma inguinale of the cervix, consisting of a large cauliflower mass of soft, friable, bleeding tissue. Note the close resemblance of the lesion to cervical malignancy.

## HISTORIC

Since McLeod<sup>1</sup> first described granuloma inguinale in 1882, numerous reports dealing with its clinical and pathologic aspects have appeared in the literature. D'Aunoy and von Haam,<sup>2</sup> in a recent extensive review of the subject, were able to collect 251 cases, to which they added 294 of their own. They feel that the condition is endemic in the South, and state that the problems of its diagnosis and epidemiologic control are far from being solved.

Gardner,<sup>3</sup> in 1928, was the first to suggest that the exuberant granulomatous ulcerations of the cervix, nonmalignant in character, which had been described by several investigators might be related to granuloma inguinale. Six years later McGee<sup>4</sup> reported eight such lesions from Charity Hospital of Louisiana. He pointed out that the clinical appearance and histopathology in these cases were strongly suggestive of granuloma inguinale, and that their favorable response to tartar emetic therapy was identical with the response of true granuloma inguinale to this type of treatment. He was unable, however, with the staining methods at his disposal, to demonstrate Donovan bodies in the tissues, and he was therefore forced to classify the cases as nonspecific cervical granulomas. It is interesting to note that by the use of the improved staining methods available to us, when we began our study, we were able to demonstrate Donovan bodies in four of McGee's eight cases, and so to confirm the diagnosis of granuloma inguinale which he had suggested.

In 1937, by the report of two proved cases, Pund and Greenblatt<sup>5</sup> established granuloma inguinale of the cervix as a distinct clinical entity. Since then, so far as we have been able to ascertain, 12 additional cases have been reported in the literature.<sup>6, 7</sup> Our own experience, as we have already intimated, has convinced us that this lesion is by no means as infrequent as the small number of reported cases would lead one to believe. Indeed, we are convinced that a more frequent recollection of the condition, with a more general use of biopsy and of a careful staining technique, would reveal the diagnosis in many suspicious lesions of the cervix.

## PATHOLOGIC ANATOMY AND HISTOLOGY

It is now generally agreed that granuloma inguinale should be regarded as a venereal infection, even though extragenital lesions have been described, including one instance of involvement of the larynx and another of involvement of the bowel.<sup>8-10</sup> In the female the usual site of predilection is the skin and subcutaneous tissues of the external genitalia and of the perineal and inguinal regions.

D'Aunoy and von Haam, on the basis of their analysis of their 545 collected and personal cases, divided the lesions into five principal groups, according to the clinical appearance and histopathology. They also concluded that the disease is a strictly local infection, with no dissemination of the infectious agent and no toxic manifestations unless secondary infections occur. Such secondary infections, they point out, must always be regarded as very serious.

The Donovan body, which is the specific etiologic agent in granuloma inguinale, is a microorganism which probably belongs to the protozoan group, although there is some evidence to suggest that it may be a fungus. It is pathogenic only for man and is transmitted only by direct contact. It has never been cultured. The incubation period is thought to be forty to sixty days.<sup>11</sup>

The lesion of granuloma inguinale of the cervix appears first as a soft, red, granular macule (Fig. 1). It enlarges rapidly and sometimes ulcerates early, forming a shallow, granular ulcer with well-defined edges. Sometimes it develops as a hypertrophic granular mass in which are numerous small areas of ulceration. In advanced stages the entire cervix may be replaced by a large cauliflower mass of soft, friable bleeding tissue (Fig. 2). The cervical lesion may extend to the adjacent vaginal walls and may completely fill the vaginal vault, or, occasionally, may be combined with only a few discrete vaginal lesions, or even a single lesion.

Microscopic examination of the lesion reveals characteristic exuberant granulation tissue in which the pathognomonic cell is found. There is an abundance of loose

Thirty-four patients had had from one to 12 pregnancies, and 26 had had more than 3. Only 2 had never been pregnant. Parity seems to enhance susceptibility to this infection, and the increased vascularity of the tissues during gestation, plus the added trauma of labor, seems to stimulate the lesion to rapid growth. Three patients, however, developed their disease four, ten, and twelve years, respectively, after the menopause.

In 4 cases the diagnosis was made during gestation. One of these patients aborted at two and one-half months. In the other 3 cases the lesions enlarged rapidly during the last trimester of pregnancy and in the early puerperium, and the response to therapy was poor. Five patients had extensive involvement of the cervix, associated with marked symptoms, within six weeks after parturition, and another presented herself within three months, with a cervical growth which filled the entire vaginal vault. In these 6 cases, the cervix was apparently normal during pregnancy.

A purulent or bloody vaginal discharge, hemorrhage, and pelvic pain were the chief complaints for which the patients sought relief. The earliest symptom was usually a serous discharge, followed successively by purulent leucorrhea, blood-stained leucorrhea, or, in some instances, by profuse vaginal hemorrhage. Bleeding was present in 31 of the 38 cases, the prominence of this symptom being due to the tendency of the lesion toward early ulceration, with involvement of the highly vascularized cervical tissue.

Thirty patients complained of pain or discomfort in the lower abdomen, usually associated with backache. The pain was bilateral in all but four instances. Many patients exhibited parametrial and adnexal thickening and tenderness upon pelvic examination, and eight had palpable masses in the pelvis. In many, if not in most cases, the pelvic inflammatory disease was concomitant or pre-existent, and not the result of the cervical infection, for a large percentage of the colored women treated at Charity Hospital exhibit pelvic disease. In other instances the associated pelvic disease was apparently due to secondary infection of the primary cervical lesion, with lymphatic extension to the pelvis. Direct extension of the granuloma inguinale to the pelvis may also occur, with involvement of the uterus, tubes, and ovaries.<sup>12</sup>

Ten of the 18 patients who were hospitalized had temperatures above 100° F., and 14 had sedimentation rates of less than thirty minutes. Many were anemic and complained of weakness, thus demonstrating the effects of blood loss and of chronic infectious processes.

The duration of symptoms varied from one week to three years. Most of the long-standing cases represented untreated or chronic lesions, or perhaps recurrences, rather than re-infections. About one-half of the patients sought relief in less than a month after the onset of symptoms, apparently because of the foul-smelling, sanguinopurulent discharge which caused sufficient discomfort to force them to seek early medical consultation. The interval is unusually short for colored patients who tend to delay medical consultation whenever severe pain is not a prominent symptom.

The lesion was limited to the cervix or the cervix and upper vagina in 28 of the 38 cases, but ulcerations were also present on the cervix and vulva in 5 cases, on the cervix and about the perineum and anus in 3, and on the cervix and in the inguinal region in 1. We also observed 1 patient in whom the infection involved the cervix and vagina, the perineal and anal regions, and the inguinal region. Concomitant infections of the cervix and of other sites by granuloma inguinale are thus not rare. In 4 of the 10 cases in which other sites were also involved, the cervix seemed to be the primary site of the infection. In the other 6 cases, sites other than the cervix were involved first.

#### DIAGNOSIS

The differential diagnosis of cervical granuloma inguinale offers considerable difficulty and the percentage of error is high. This is not unexpected, for the symptomatology and gross appearance of the lesion closely simulate those of other diseases. In this series only 8 of the 38 cases were diagnosed correctly by clinical means. In 27 cases a tentative clinical diagnosis of carcinoma was made; the

connective tissue in which are many young blood vessels. The lumina of these vessels may be completely filled with polymorphonuclear leucocytes. The granulation tissue is interspersed with large numbers of plasma cells and a diffuse infiltration of polymorphonuclear leucocytes, which often appear as large, dense collections. There is usually a relative absence of lymphocytes.

The essential feature of the histopathology is the presence of large monocytes with many intracytoplasmic spaces in which the Donovan bodies are dispersed. These bodies, which are elliptical or round and stain deeply, are usually arranged peripherally in the intracytoplasmic spaces. Sometimes, however, they are scattered through the cell, or appear as one or more collections, pushing the nucleus to the side. Sometimes, again, the entire cell may be filled with closely packed organisms which completely obliterate the cell outline, and extracellular clusters may be visible. In addition to the Donovan organisms, various spirochetes and motile fusiform bacilli are frequently noted. Secondary invasion by other bacteria is also common (Fig. 3).

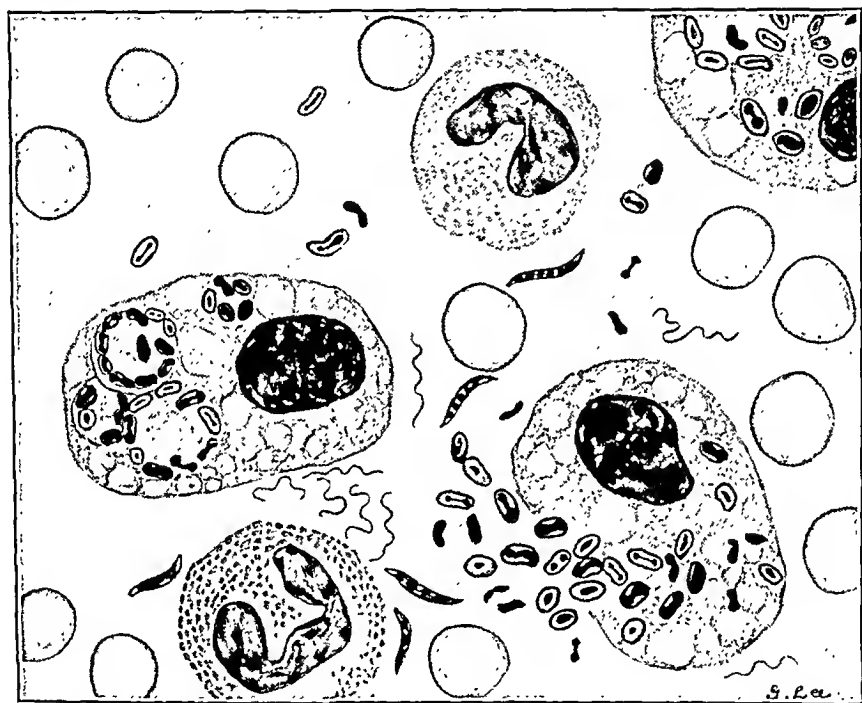


Fig. 3.—Composite camera lucida drawing ( $\times 2,000$ ) to illustrate: *a*, Relative size and structure of typical large mononuclear endothelial cells and Donovan bodies. *b*, Characteristic arrangement of Donovan bodies around periphery of intracytoplasmic spaces of monocytes. *c*, Extracellular organisms. Note encapsulated and nonencapsulated ovoid form and intense bipolar staining reaction. *d*, Associated gram-negative, motile, fusiform bacilli and spirochetes.

#### ANALYSIS OF CASES

Thirty-four of the 38 patients were colored and only 4 white, these figures being in agreement with the high proportion of negroes with granuloma inguinale of the external genitalia reported in the literature. Apparently these are the first cases of cervical granuloma inguinale to be reported in white women. The predilection of the disease for the negro race is probably to be explained by the difference in sex hygiene and moral standards in the colored and white races, since promiscuity in sex relations and unhygienic conditions of the genital organs have been established as contributory or predisposing causes of granuloma inguinale.

Thirty-one patients were between 20 and 40 years of age, which is the period of maximum sexual activity. The age range was from 18 to 62 years; the oldest and youngest patients were negroes.



of 1 per cent solution. Local therapy is also advised in all cases. We have had the best results with topical applications of neoarsphenamine (4.5 per cent) in glycerine to combat fusospirochetosis and secondary infections and to promote healthy granulation tissue. We also employ potassium permanganate irrigations (1:1000 solution) to alleviate local irritation and to overcome the odor of the discharge.

Of the 27 patients in this series who were placed on tartar emetic therapy, 6 failed to continue treatment and were lost sight of. Of the 21 who received adequate treatment, 17 exhibited healthy cervixes when treatment was discontinued. In most cases clinical improvement was noted within three to four weeks after treatment was begun. In one instance cure was effected by four injections of tartar emetic given over a four weeks' period, but the average duration of treatment was three months. The longest course of treatment was fourteen months.

It is most important that treatment be continued long enough to effect a permanent cure; the tendency is to discontinue it when signs of superficial improvement are evident. Chronic lesions are often resistant to therapy, but early lesions usually respond rapidly, and prompt diagnosis is therefore essential to a rapid cure. In a few cases spontaneous cures may follow the control of secondary infections by topical applications, but this is not usual. Recurrences with any form of therapy are unfortunately common.

Five patients in our series, one of whom had previously failed to respond to tartar emetic therapy, had large, fungating cervical masses which were treated by excision of the mass with the actual cautery knife, or the electrosurgical unit preliminary to intensive treatment with tartar emetic. When these methods are used, it is important that the line of excision should extend well beyond the infected tissue. Bleeding is readily controlled by coagulation of the base of the lesion.

Two patients were treated with deep x-ray therapy and both responded rapidly, but failed to continue treatment and no follow-up data are therefore available. We have gained the impression, however, that this method deserves a more extensive trial. One patient, who had fibroids of the uterus and pelvic inflammatory disease also, was treated with tartar emetic for two months, and then was submitted to complete hysterectomy and bilateral salpingo-oophorectomy. Pund and Gotcher<sup>12</sup> have reported a somewhat similar case in which sections of the uterus and adnexa revealed characteristic Donovan bodies, but in this case they were found only in the cervix.

At the present time we are treating a patient with granuloma inguinale of the cervix by sulfanilamide, using the drug orally and applying it locally as a heavy coating of powder. The results have been striking and seem to justify a further careful trial of sulfanilamide therapy.

The therapy of granuloma inguinale of the cervix during pregnancy demands a special note, for, as we have already stated, the response to tartar emetic therapy is poor. Large growths may complicate labor and introduce serious hazards of hemorrhage and infection. Delivery from below should always be employed if it seems safe. If, however, the cervical growth is extensive or if concomitant lesions of the external genitalia have produced so much scar tissue that vaginal delivery seems unwise, Porro cesarean section may be necessary. We are at present observing a patient who will require this operation, because the large masses of granulatous tissue in the perineum, vulva, and vagina will make delivery from below impossible.

The obvious maternal hazards of granuloma inguinale in pregnancy should not blind us to the child's risk. Dr. J. K. Howles<sup>14</sup> has recently brought to our attention a case in which, presumably, the disease was transmitted to the baby during delivery. The mother, a negro woman, had extensive granuloma inguinale of the vulva and perineum, and six weeks after delivery the baby was observed to present the same condition at the umbilicus. The lesions were extremely resistant to treatment, and cure was not effected until some eighteen months had elapsed. We had not previously considered the possibility of such transmission, but there seems no reason, upon reflection, why under these circumstances granuloma inguinale should not be transmitted by contact as readily as gonorrhea is. We do not recollect having seen this possibility mentioned anywhere in the literature on the subject.

diffuse redness and softened consistency of granuloma inguinale are significant diagnostic points in this connection, though it must also be remembered that granulomatous lesions containing large amounts of fibrous tissue may appear hard and nodular. Two cases were diagnosed as everted cervical erosions, and one was diagnosed as chorionepithelioma because of post-partum bleeding of three months' duration and the presence of a large cauliflower mass attached to the cervix, with fixation of the uterus.

In addition to the diseases already mentioned, granuloma inguinale of the cervix must be distinguished by appropriate tests and examinations from all other conditions causing granulomatous lesions of the cervix. These include lymphogranuloma venereum, chancroid, syphilis, and tuberculosis. The mixed venereal infections which are frequently present in combination with granuloma inguinale may also seriously confuse the picture. Eighteen of the 38 patients in our series had syphilis, 9 had active gonorrhea, and 4 had both diseases.

Each suspected case of cervical involvement should be studied according to the following routine:

1. Wassermann reaction for syphilis.
2. Dark-field examination for spirochetes.
3. Smears and cultures for gonococci.
4. Frei test for lymphogranuloma inguinale.
5. Intradermal antigen test for chancroid.
6. Biopsy for tuberculosis, nonspecific granulation tissue, malignancy, and granuloma inguinale.

The final diagnosis in all cases in this series was made by the demonstration of Donovan bodies in a biopsy specimen. In some 20 additional cases the gross and microscopic picture and the response to therapy were strongly suggestive of granuloma inguinale, but typical Donovan bodies could not be identified in the cervical tissues, and these cases have therefore been omitted from this analysis. No matter how suggestive the clinical and histopathologic picture may be, no case should be accepted as granuloma inguinale unless the pathognomonic cell is found.

Demonstration of the Donovan bodies, which is essential for diagnosis, is by no means a simple matter in many cases, particularly if the histologic technique employed is inadequate, or if the material examined is insufficient. Often, because of the chronicity of the lesion, only a few monocytes may be present in the sections. The monocytes may be confused with large plasma cells containing deep-staining, fragmented nuclei, and the Donovan bodies may be confused with debris. It is apparently more difficult to demonstrate Donovan bodies in material from mucous membrane surfaces than from the more usual sites in the skin and subcutaneous tissues. As we have already pointed out, no culture methods are available. These difficulties should be emphasized, for the literature is often misleading and gives the impression that the pathognomonic cells can always be easily identified, whereas actually a diligent search of many sections may be necessary before the diagnosis can be confirmed.

We have had better results by the use of tissue sections secured by biopsy than by the use of scrapings or smears. The biopsy should include the base of the lesion, for often necrosis and secondary infection in the more superficial areas obscure the specific histology. We also prefer formalin-fixed paraffin sections to celloidin sections or frozen sections. Dieterle's<sup>13</sup> silver stain, in our experience, is the most accurate of the various staining techniques. Donovan bodies have a marked affinity for silver salts and often can be demonstrated readily by this method while remaining persistently invisible by other staining techniques. It is usually possible to demonstrate them by hematoxylin and eosin staining and by Wright's stain, with Zenker fixation, although they are often considerably less distinct, we have found, when these methods are used.

#### THERAPY

Antimony compounds are considered specific in granuloma inguinale and should be employed routinely, although, if special indications are present, it may be necessary to employ other measures also. We personally prefer tartar emetic to fuadin. It is given intravenously twice or three times a week, in doses of 10 c.c.

improvement in the appearance of the cervix, and the pelvic pain was somewhat decreased. The cervical lesion became progressively smaller, and clinical improvement was steady. At the end of the eighth week of treatment the cervical lesion had disappeared entirely, and examination ten months later revealed a normal cervix.

### SUMMARY

1. Thirty-eight cases of granuloma inguinale of the cervix were observed at Charity Hospital of Louisiana during the ten-year period ending July 1, 1939, 21 of the number being identified within the last two years. Four of the patients were white, and represent the first instances of this disease to be reported in white women.

2. The clinical and histopathologic features of the lesion are discussed. The diagnosis is dependent upon the demonstration of the pathognomonic cell-containing Donovan bodies, which are most readily identified by the use of fixed biopsy material and the silver impregnation method of Dieterle.

3. Carcinoma of the cervix is easily confused with cervical granuloma inguinale, and 27 of the 38 cases in this series were so diagnosed. The close clinical similarity of the two conditions is responsible for the error.

4. Vaginal bleeding and pelvic pain were the outstanding symptoms.

5. Intravenous antimony therapy is the most effective form of treatment, and tartar emetic gives the best results. The duration of treatment is shortened if large growths are completely excised by means of the cautery knife before specific therapy is begun. Recurrences are common.

6. Granuloma inguinale of the cervix is a clinical entity which demands general recognition and further study. Only by these means will the true incidence be established and improved methods of diagnosis and treatment be evolved.

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### DISCUSSION

DR. EDWIN L. ZANDER, NEW ORLEANS, LA.—The Charity Hospital of Louisiana at New Orleans affords a unique opportunity not only for the investigation of unusual pathology but also for the comparative study of various diseases in the negro and white races. It is not surprising, therefore, that the authors have been able to find at Charity Hospital 38 cases of granuloma inguinale of the cervix. Nor is it surprising, in view of the predilection of other forms of this disease for the colored race, that 34 of the 38 cases should have occurred in negro women.

## MORTALITY

Two of the 38 patients died, a mortality of 5.2 per cent. One, in the early years of this study, was treated by local acetone applications, to which she did not respond. She continued to bleed from the vagina and became progressively weaker until death. The other patient was treated by the application of 4,800 mg. hr. of radium. She was discharged from the hospital as improved, but died shortly afterward of profuse hemorrhage from the cervix. Both these deaths make it clear that granuloma inguinale should not be considered an innocuous disease, and make clear also the importance of early diagnosis and adequate therapy.

## CASE REPORT

The following case report is cited as typical:

L. G. (No. 57238), a colored woman 23 years of age, para iii, was seen in the Outpatient Clinic of the Charity Hospital of Louisiana at New Orleans, June 21, 1938. She complained of a bloody vaginal discharge and of low abdominal pain of four weeks' duration. Her last pregnancy had terminated ten months previously.



Fig. 4.—Biopsy section of cervical lesion (Case 57238) stained by the silver impregnation method of Dieterle. The exuberant granulation tissue contains pathognomonic cells with Donovan bodies in circular arrangement about intracellular cysts. Dark-staining, rodlike, Donovan bodies are dispersed in other cells but are not readily identified in this focus.

The whole cervix was found to be diffusely reddened. The upper lip was almost entirely replaced by an exuberant mass of soft, granular tissue which bled easily on manipulation. On pelvic examination the uterus was normal in size and position, but was somewhat tender on movement. Both adnexal regions were tender to palpation, and a soft mass, 5 cm. in diameter, was palpated in the right adnexal region.

The patient's temperature on admission was 99.4° F. The red blood cell count was 3,100,000 and the hemoglobin 70 per cent. The Wassermann and Kahn reactions were negative. Smears from the cervix and urethra revealed no gonococci, and the Frei antigen test was negative. The sedimentation time was ten minutes.

The tentative diagnosis was subacute pelvic inflammatory disease and granuloma inguinale of the cervix. Biopsy of the cervix revealed characteristic Donovan bodies (Fig. 4).

Treatment consisted of the intravenous injection of 10 c.c. of 1 per cent solution of tartar emetic twice weekly, combined with topical applications of 4.5 per cent neocarsphenamine in glycerin. At the end of three weeks there was a decided

## FURTHER STUDIES ON THE ANDROGEN THERAPY OF GYNECOLOGIC DISORDERS\*

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IT HAS conclusively been shown that testosterone, the male hormone, or its derivative, testosterone propionate, is capable of inducing progestational-like proliferation of the endometrium of rabbits and rats.<sup>1</sup> Like progesterone it will inhibit uterine contractions induced by estrin,<sup>2</sup> maintain pregnancy following the excision of the ovaries, and delay parturition in the normal pregnant rat.<sup>3</sup> Furthermore, it is effective in neutralizing vaginal and uterine responses to estrin and is capable of completely suppressing spontaneous estrus cycles in rats and mice.<sup>4</sup> It is significant that testosterone propionate is four to eight times more active than progesterone in this latter reaction, being effective in doses of 0.05 to 0.1 mg. daily.<sup>5</sup>

Other effects have been obtained in primates by injections of testosterone propionate. Zuckerman<sup>6</sup> induced ovarian atrophy and endometrial involution in monkeys while menstruation was completely suppressed throughout the duration of treatment. In normal women, Hartman<sup>7</sup> and Papanicolaou, Ripley and Shorr<sup>8</sup> have obtained similar results.

It was suggested that some gynecologic disorders which on a theoretical basis should respond to progesterone, might also respond to androgenic therapy. In this regard painful breasts and dysmenorrhea first received the attention of gynecologists.

Desmarest and Capitaine<sup>9</sup> reported excellent results in these conditions. The ability of testosterone to suppress menses suggested its application in the treatment of excessive uterine bleeding. Loeser<sup>10</sup> injected doses of 50 mg. of testosterone propionate every other day to patients with menorrhagia and was able to control the flow. He maintained that about 500 mg. during the month was necessary to suppress the menstrual bleeding until the next period, while 300 mg. postponed the menses for about eight to ten days. Biopsies of the endometrium revealed that this tissue had undergone atrophy. Loeser noted also that fibromyomas decreased in size significantly under this therapy. He obtained beneficial responses also in two cases of chronic cystic mastitis and in several cases of dysmenorrhea, using somewhat smaller doses (150 to 300 mg.).

Additional information regarding the therapeutic value of testosterone propionate was reported by Foss<sup>11</sup> who treated 16 cases of excessive menstrual bleeding of functional origin with excellent results in most instances. The dosages which he administered were quite large, 300 to 800 mg., and he injected as much as 2,000 mg. in resistant cases. Ovulation was inhibited as indicated by endometrial biopsies. Foss noted that several patients under androgenic therapy developed hot flushes and other symptoms of the menopause. The beneficial effect of testosterone on excessive bleeding has been further confirmed by Geist, Salmon and Gaines,<sup>12</sup> who obtained gratifying results in 24 out of 25 cases and by Mazer and Mazer<sup>13</sup> who reported excellent results in uterine bleeding.

\*Presented at the Eleventh Annual Meeting of the Central Association of Obstetricians and Gynecologists, Kansas City, Mo., November 2 to 4, 1939.

Any clinician working in a large gynecologic clinic will see at not infrequent intervals extensive ulcerations of the cervix. A definite diagnostic routine has been set up at the Charity Hospital for the study of suspicious lesions: (1) Wassermann and Kahn for syphilitic gumma; (2) dark-field examination for chancre; (3) smears and cultures for gonorrhea and pyogenic organisms; (4) wet mounts for trichomonads and yeast; (5) skin tests for lymphogranuloma inguinale and chancroid; (6) biopsy for malignancy, tuberculosis, nonspecific infection, and granuloma inguinale.

Although antimony compounds are considered specific in treatment, I believe that there is a definite tendency for spontaneous cure if secondary infection can be controlled. The toxic effect of antimony in large doses is well known.

Dr. Arnell has shown that by careful examination granuloma inguinale of the cervix is not as rare as it was supposed to be prior to our improved methods of diagnosis and knowledge of its clinical entity.

DR. HERBERT E. SCHMITZ, CHICAGO.—I would like to add one case which demonstrates the necessity of differentiating these lesions from carcinoma of the cervix. The patient, a colored woman, aged 26, entered the Obstetrical Department of the Cook County Hospital one year ago. She was delivered by Dr. Kobak, at which time he noticed an indurating lesion of the cervix. Thinking of the possibility of carcinoma, he transferred the patient to the Tumor Service. I took a biopsy, made a clinical diagnosis of carcinoma, and had the patient admitted to the ward for radium therapy. She was given 3,500 mg. hours. She left the hospital and did not return until two weeks ago. She now has an extensive lesion, involving the entire vagina and vulva, and is in a very critical condition. Since that time six biopsies have been taken and each time Dr. Schiller has returned a diagnosis of nonspecific granuloma.

DR. EARL CONWAY SMITH, NEW ORLEANS, LA.—One immediately is reminded of the lack of information concerning the true incidence of the disease. We have begun to wonder whether all granular lesions of the cervix should be subjected to the silver stain method, or some procedure that is practical for the diagnosis of this condition.

Our attention must also be directed to the chief points in the pathologic picture of cases of granuloma inguinale, involving the external genitalia that have, for one reason or another, become chronic. Here, we find granulation tissue, secondary infection, and a very definite attempt by nature to heal the lesion. It is because of this pathologic picture that, in cases complicating pregnancy, we select the transabdominal route for delivery to avoid serious results that would follow the vaginal route.

DR. ARNELL (closing).—We have often found it difficult to demonstrate the Donovan bodies after tartar emetic has been given. In several cases it was impossible to find the Donovan bodies two weeks after therapy had been administered. It is essential to get to the base of the lesion as the superficial necrotic tissue does not contain Donovan bodies.

gen. It is apparent that the mechanism by which testosterone propionate produces these changes is not through its progestational action, since changes typical of progesterone have not been demonstrated in the endometrium but through suppression of ovarian activity. It is not unlikely that the therapeutic results which are claimed for progesterone itself are due to this response rather than that on the endometrium. As a matter of fact, the significance of endometrial changes in ovarian dysfunction has been frequently postulated but never conclusively demonstrated for such common disorders as menorrhagia or dysmenorrhea. One may find any stage of endometrial development from the resting phase to the secretory. The fact that normal secretory endometrium is frequently found in patients with excessive menstrual flow indicates that this bleeding is not due to the lack of corpus luteum activity as is frequently postulated. Hence, the proposed therapy of this condition with progesterone is not on a sound basis. In reality, evidence indicates that relatively large doses of progesterone, amounting to 100 mg. or more in the last ten days of a cycle, are usually ineffective in controlling uterine bleeding.<sup>17</sup> The concept that functional bleeding is due to endometrial hyperplasia might also be abandoned, since it has been sufficiently demonstrated that hyperplasia is not as frequently associated with menorrhagia as formerly believed. In fact, hyperplasia is often seen in cases of amenorrhea or in women with normal menstrual cycles. The attempt to control excessive flow should therefore not consist primarily of attempting to alter the endometrium, since it seems quite possible that there is no correlation between excessive bleeding and histologic changes of the endometrium. It is our belief that we must look elsewhere than the endometrium for the etiology of these ovarian dysfunctions and the explanation for the therapeutic responses in these conditions.

The mechanism by which testosterone propionate influences the ovarian function in human beings has been suggested by Foss to be through its action in suppressing pituitary activity, on the basis of the endometrial changes which he obtained in the human being. Geist has considered the "modus operandi" of this substance somewhat complex and in some respects paradoxical. For instance, testosterone in primates induces ovarian inactivity and subsequent involution of the accessory sex organs, while in the rodent, it produces progestational proliferation, uterine hypertrophy, and persistent corpora lutea in the ovaries.

These seemingly contradictory findings have, however, been explained by Freed, Greenhill, and Soskin,<sup>5</sup> who have demonstrated a biphasic effect of testosterone propionate on the pituitary of the rat. Small amounts were found to inhibit the pituitary follicle-stimulating hormone resulting in ovarian atrophy and subsequent uterine involution due to lack of estrin. Large doses released the luteinizing hormone resulting in persisting corpora lutea and a similar suppression of estrin. The uterus underwent hypertrophy however, due to the fact that a large dose of androgen is capable of acting directly on the uterus in the absence of estrin as in the castrate rodent. It was suggested there-

In a preliminary report we recorded our results in 22 patients with various menstrual disorders.<sup>14</sup> At that time we obtained beneficial results in patients with functional menorrhagia when the injections of 25 to 50 mg. testosterone propionate were administered during an entire month and in dysmenorrhea when the injections were given during the second two weeks of the menstrual cycle. The present paper deals with a follow-up of the patients who responded satisfactorily and includes results on 12 additional patients who have been treated recently.

## RESULTS

*Old Cases.*—In a group which consisted of four dysmenorrheic patients who received androgen during the second two weeks of their menstrual cycle, one patient had complete relief, two had moderate, and one slight relief. The patient with complete relief experienced painful periods three months following cessation of treatment, and one of the two patients with moderate relief also complained of a return to her painful periods after several months. The other patient has had appreciable relief for almost one year.

The group of eight patients who received 25 to 50 mg. testosterone propionate for one month or longer were re-examined. One patient who was dramatically relieved of dysmenorrhea and menorrhagia due to fibroids, had normal periods for three months, then pain and bleeding returned as before therapy. The fibroid is now definitely larger than before. Another patient with severe functional menorrhagia and dysmenorrhea had eight normal periods. Then every other period became painful but not as severely as before therapy. The bleeding is again excessive but not to the degree existing before the injections.

Of the other patients in this group who responded favorably, two had endometrial hyperplasia with menorrhagia and two had small fibroids with menorrhagia. They responded satisfactorily at the time of treatment and have remained in good condition for the past seven to twelve months.

*New Cases.*—Twelve patients have been more recently receiving testosterone propionate.\* This group consists of three patients with functional menorrhagia, one with menorrhagia and dysmenorrhea, three with menometrorrhagia, one with premenstrual migraine, and four with painful breasts preceding the menses. The patients with uterine bleeding received testosterone propionate in 25 to 50 mg. injections three times weekly for one month, and those with painful breasts and migraine were given injections only during the last two weeks of the cycle. Our results with these patients were even more satisfactory than in our preceding series. Except for one patient with menometrorrhagia all were markedly benefited immediately following therapy. Bleeding was checked effectively, several patients having normal periods for the first time in two or three years. Breasts which ordinarily caused considerable pain produced little distress whether the trouble was due to simple engorgement or to adenosis.

One of the patients, who received 350 mg. during a month, showed a considerable degree of hirsutism and acne but no lowering of the voice.

## DISCUSSION

Our results confirm the observation of others that in the human being, testosterone propionate inhibits ovarian activity with the suppression of uterine bleeding and involution of the accessory sex organs, including the breasts, uterus, and vaginal mucosa. Fibromyomas, which are also under the influence of the ovary, regress. These anatomic changes persist only as long as the patient is under the influence of the andro-

\*We are indebted to The Schering Corporation and to The Ciba Pharmaceutical Products for the generous supply of testosterone propionate.



throughout a period of a month are often necessary in menstrual disorders, especially in menorrhagia and somewhat less in mastopathies. It is quite probable that the obstacles to administering these large doses will soon be overcome with the progress now being made in the chemistry of androgens.

Caution should be exercised in administering testosterone propionate as it has already been demonstrated that virilism (hirsutism, change in voice and slight enlargement of the clitoris) can be induced in some women who receive large doses of this substance.<sup>16</sup> Likewise some women gain weight and develop an acneform eruption. However, most of these disagreeable side-effects disappear slowly after the hormone treatment is stopped, but some may persist for six months or longer. These undesirable features of androgenic therapy may possibly be eliminated with the development of newer preparations which may retain the effectiveness of testosterone propionate but not the masculinizing activity of this substance.

#### SUMMARY

A follow-up of patients treated from seven to twelve months previously with testosterone propionate for gynecologic ailments with satisfactory results, revealed that more than 50 per cent continued to derive appreciable benefit after discontinuing the therapy. The patients with dysmenorrhea tended to relapse more often than those with excessive uterine bleeding but the smallness of our series of patients does not permit more definite conclusions. Twelve additional patients who were treated more recently, and of whom three had menorrhagia, one had menorrhagia and dysmenorrhea, three had menometrorrhagia, four had painful breasts, and one had premenstrual migraine, responded satisfactorily to androgen therapy except in one case of menometrorrhagia. The only disturbance observed occurred in a patient who received 350 mg. of testosterone propionate in one month and who developed considerable hirsutism and acne.

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#### DISCUSSION

DR. PHILIP F. SCHNEIDER, EVANSTON, ILL.—Of the endocrine substances we have used the one that has been the most uniformly successful has been insulin in the treatment of diabetes. The satisfactory results obtained are due to the

fore, that the involutionary changes in the reproductive organs of human beings resembled the reaction to the small doses of androgen in the rat. The doses chosen for therapy are apparently relatively small for the human being when compared to experimental animals. The findings of Engle and Smith<sup>15</sup> that 25 mg., but not 5 or 10 mg., of testosterone propionate injected daily is capable of inducing a progestational endometrium in monkeys support these conclusions.

From our results and those of other workers in this field, it is not unreasonable to conclude that male hormone therapy has definitely beneficial effects in certain ovarian disorders. At the present time testosterone propionate has been used with promising results in mastopathies, menorrhagia, and dysmenorrhea.

In the treatment of dysmenorrhea and painful breasts, suppression of the menses is not necessary to obtain the desired results. It seems that complete ovarian suppression is not essential for some therapeutic responses, and it is possible that the direct antagonism of estrogen by the male hormone plays a role in the treatment of mastopathies and dysmenorrhea.

This neutralizing property of testosterone propionate has been demonstrated both in histologic responses of estrogen and in its myometrial activity. It is possible that the alleviation of dysmenorrhea is on the basis of inhibiting uterine muscle contraction. This explains the results obtained in our cases with the injection of 150 to 250 mg. of testosterone propionate in the last two weeks of the cycle wherein the pain was relieved but the menses were not disturbed. This dosage may, in certain cases, be insufficient, however, and injections during the entire month may be required in the severe cases to induce a temporary menopause in order to relieve the pain.

In the treatment of menorrhagia it seems fairly conclusive that large amounts are required so that ovarian activity is completely suppressed. We have observed several cases where sufficient testosterone propionate was administered to prevent ovulation as detected by endometrial biopsies, but this did not prevent or delay the menses significantly. In our limited experience, ovulation can be inhibited with approximately one-half the amount necessary to suppress menstruation (anovular menstruation).

While it is apparent that testosterone propionate has an effect on the pituitary gland and ovaries, it is still not understood why beneficial responses often continue following cessation of testosterone propionate injections. The explanation must await further investigations as to the mechanism of menstruation and the etiology of menstrual disorders. It is difficult to conclude from our small series how lasting the results will be; but it is our impression that the results have been fairly satisfactory from the standpoint of permanence. We will be in a better position for more definite conclusions after following the results obtained more recently.

From a practical standpoint, it is apparent that though moderate doses may frequently be effective, doses of at least 300 to 500 mg.

organs even though these alterations may not be demonstrable under the microscope. We do know that many women have nausea and vomiting following the use of stilbestrol and in some animals, liver damage has been demonstrated after administration of large doses of this substance.

Notwithstanding the fact that many of us have obtained good results in some gynecologic disorders, we should not recommend the indiscriminate use of the male hormone or stilbestrol by general practitioners.

## POST-PARTUM LABIAL OR PARAVAGINAL HEMATOMAS\*

HUGH G. HAMILTON, KANSAS CITY, MO.

**L**ABIAL or paravaginal hematomas are unusual complications of the puerperium, but when they do occur, they can present a very serious situation unless diagnosed early and actively handled. The first report of such a case is by Rueff in 1554. The literature on the topic is not voluminous, and there are relatively few cases to be found reported.

These hematomas may be divided into two groups, the immediate and the delayed. The immediate type occurs as soon as the labor is finished and is usually considered traumatic, though this is not actually correct.

In this connection Frank-Kamenetsky<sup>1</sup> reports four cases of twin delivery in which the hematoma manifested itself during the time between the delivery of the first and second baby. The delayed type is usually due to necrosis of the blood vessels and may occur as late as twenty-one days post partum. DeLee<sup>2</sup> reports one case occurring this late. Manzi<sup>3</sup> reports a case of chorionepithelioma which very closely resembled the delayed paravaginal hematoma.

The symptomatology in either type of case and the prognosis and treatment are essentially the same. Since the hemorrhage occurs in a soft, bruised tissue, there is widespread dissection, and the most striking symptom is excruciating pain, which is not relieved by reasonable doses of opiates and becomes progressively more severe. If the hemorrhage occurs external to the pelvic fascia and the levator ani muscles, the dissection is downward, and there is, first, unilateral labial and vulvar edema followed by the appearance of a bluish, discolored mass which is painful, elastic, tense, fluctuating, and extremely sensitive to palpation. This mass may extend back into the ischiorectal fossa and over into the buttock and, if allowed to increase in size, may displace the anus, perineum, and vagina over to the opposite side.

If the hemorrhage occurs above the level of the pelvic fascia and the levator ani muscles, the patient will have the same severe pain, and coupled with this will present usually the unilateral edema due to circulatory interference by compression. Rectal and/or vaginal exami-

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purity of the substance and to the availability of blood sugar determinations as a guide for therapy. The estrin and progestin preparations that have been available for a number of years are pure ovarian substances, and we believe that vaginal smears and subjective symptoms may be utilized in the same manner as the blood sugar in the treatment of diabetes as guides.

We are told never to give estrin in large or in long-continued dosage to women prior to the menopause, because of the danger of producing ovarian atrophy. We know that if you give estrin to a woman who has normally functioning ovaries that atrophy will probably occur, but in the woman who has an estrin deficiency, ovarian atrophy already exists and adequate estrogenic therapy will not only not increase ovarian atrophy but will restore ovarian function to an approximation of the normal. This observation is based on vaginal smear control.

DR. KARL JOHN KARNAKY, HOUSTON, TEXAS.—At the menstrual disorder clinic of the Jefferson Davis Hospital in Houston we have used all the hormones and other drugs commonly advocated for dysmenorrhea and menometrorrhagia, but for some time obtained our best results with testosterone propionate. One of my young patients developed a coarse voice and one developed a visible mustache, both of which passed away within six weeks to six months.

By the use of stilbestrol, however, we have obtained most excellent results in our menorrhagia cases. The patient is given ten 5 mg. tablets and told to take one every night, beginning two or three days before the expected period. The period is then missed altogether, is delayed and shorter, or else the patient will spot for one to three days. The blood loss is decreased 95 per cent. The cost of such therapy is about seventy-two cents. There are no injections and the patient need not come to the office. The same amount of male sex hormone would cost thirty to thirty-five dollars, and our results are far better with stilbestrol than with male sex hormone.

Stilbestrol in 15 to 25 mg. doses will stop menorrhagia in a shorter time than that required to take the patient to the hospital, prepare the operating room, and do a dilatation and curettage. We now have a very potent drug, and if we so desire we can keep a woman from menstruating or bleeding as long as we deem necessary by giving 5 to 10 mg. of stilbestrol at night. No bleeding is produced when 5 mg. (125,000 I.U.) are given each day, but if the drug is stopped there follows in one to four days a spotting which lasts for one to eight days.

Leiomyomas of the uterus and polyps of the endometrium are also controlled by stilbestrol. One now can give 15 to 25 mg. and control the flooding from these sources, thereby saving an emergency operation as well as the loss of vital blood. When 25 mg. of stilbestrol are given, the follicles become hemorrhagic which may lead to moderate pains in the ovarian regions. In twelve cases of incomplete abortion bleeding stopped by the treatment employed in other uterine bleeding cases. Six cases of increased bleeding at delivery were checked by giving stilbestrol as outlined.

DR. M. EDWARD DAVIS, CHICAGO, ILL.—We have had considerable experience with the use of testosterone propionate in very moderate doses, and in general we can confirm all the findings of Dr. Greenhill.

During the past year we have administered stilbestrol orally to some 200 patients in need of estrogenic medication. There is no need to use the tremendous doses suggested by one of the discussants. Usually, one milligram administered daily, orally, is sufficient entirely to replace ovarian activity. There has been considerable discussion concerning the toxicity of this substance. We have under way a number of experiments on the long-continued administration of moderate amounts of stilbestrol in an attempt to determine the possibility of late undesirable effects. Thus far, the moderate amounts used clinically have produced no evidence of toxicity.

DR. GREENHILL (closing).—I believe that Dr. Karnaky is much too enthusiastic about stilbestrol. Furthermore, this drug may produce disturbances in some

There is a wide variation in the incidence of this condition. DeLee<sup>2</sup> reports 1 case to 7,500, Williams<sup>5</sup> 1 case to 2,000 deliveries, and Dorland<sup>6</sup> 1 case to 1,600 deliveries. In our series it was impossible to estimate accurately the incidence of occurrence, as it includes the private practices of several men and several patients were referred to these obstetricians by other doctors.

Every obstetrician from time to time has prevented the occurrence of these hematomas, when commencing to do a perineorrhaphy, by noticing a small hematoma in one or the other side which he opened and sutured. However, it is only in these cases where suturing is practicable, for if the hematoma has been allowed to dissect at all, the original bleeding point is lost in the maze of small, bleeding, oozing vessels where the dissecting blood mass has torn along the fascial planes, damaging the venous system. Each of the authors on this subject recommends expectant treatment with compression and ice therapy in small hematomas which are not increasing in size; and incision, evacuation of clots and packing of those which are large or in which the dissection is continuing. From the results in our series and from the study of other case reports, it would seem feasible to recommend the earliest possible diagnosis and then incision, evacuation of clots, and packing in all cases. Of course, if there is shock, infection, or anemia, blood transfusions and other supportive measures should be instituted.

Coulin<sup>16</sup> reports a case where the hemorrhage dissected up into the parametrium and retroperitoneally. The patient eventually recovered upon incision, evacuation of clots, and packing. In Danby's<sup>12</sup> report one case was not drained for two days, and although she recovered she had a prolonged, febrile convalescence. In this series the only fatality was in the one case in which the so-called "expectant" treatment was used, and the patient died a septic death.

In the consideration of Williams's<sup>5</sup> series of 33 cases of which 56 per cent were fatal, the hematomas were either late in being diagnosed or the patients would not have had such massive extension of the process unless they were victims of the expectant method of treatment. The mode of death in these cases was concealed hemorrhage, or rupture of the hematomas into the peritoneal cavity or subsequent infection.

The most practical method at which one can arrive for the management of this condition then is: first, the earliest possible diagnosis; second, incision, preferably through the vaginal mucosa, into the hemorrhagic cavity; third, evacuation of the clots; fourth, loose packing of the cavity with tight packing of the vagina, and a tightly applied T-binder for compression, with removal of the packing in twelve to twenty-four hours; fifth, transfusion or other such supportive or medical measures as may be indicated.

Including our series and those of Frank-Kamenetsky,<sup>1</sup> DeLee,<sup>2</sup> Williams,<sup>5</sup> Gibbert,<sup>11</sup> Danby,<sup>12</sup> Shaw,<sup>10</sup> Coulin,<sup>16</sup> Liepman,<sup>13</sup> Hirsch,<sup>14</sup> Pio,<sup>17</sup> Polasek,<sup>18</sup> Benedetti,<sup>19</sup> D. VanVugt,<sup>20</sup> Argonz,<sup>21</sup> Moshkow,<sup>22</sup> Morosoff,<sup>23</sup> Narvaez,<sup>24</sup> and Horvath,<sup>25</sup> there is a total of 156 reported cases of post-partum paravaginal hematomas. Complete data are not available on all the cases, but the figures shown in Tables I to IV are based on 127 cases in which the data are sufficiently complete for statistical purposes.

nation will reveal an extremely tender, rounded, fluctuating, tense mass, extending into the vaginal and/or rectal space. It will dissect upward beneath Poupart's ligament, into the broad ligament and parametrial tissue and even upwards retroperitoneally to the diaphragm. When the hemorrhage becomes massive, the patient will already have shown the signs of progressive acute anemia and will now manifest the symptoms of shock due, not only to the active blood loss, but also to the tissue trauma of the dissection.

The usual concept of the etiology is that trauma is the major factor, and DeLee,<sup>2</sup> Vaux,<sup>4</sup> Williams,<sup>5</sup> Dorland,<sup>6</sup> and others hold that the immediate type is traumatic in origin. Frank-Kamenetsky<sup>1</sup> reports that 52.5 per cent of his 82 cases were of traumatic origin. Likewise there is general agreement that most delayed cases are due to pressure necrosis from prolonged compression of the vessels by the fetal head. However, these concepts do not take into consideration other factors, such as inelasticity of blood vessels (Buford Hamilton) which undergo laceration under tension without laceration of other tissues, or increased fragility of the blood vessels and hemorrhagic tendencies associated with constitutional conditions. Vaux<sup>4</sup> and Bland<sup>7</sup> mention the vascularity of the pelvic tissues at the time of delivery, with the occurrence of varicosities of the pudendal veins as an etiologic factor, but DeLee<sup>2</sup> denies the view that varicosities have anything to do with it. In our series there were no varicose veins noted in any of the cases.

Williams<sup>8</sup> describes in his work on abruptio placentae, changes in blood vessels, associated with albuminuria, which are sometimes so pronounced that the patients have an hemorrhagic tendency even in the absence of hypertension. Likewise, there are those cases of albuminuria in pregnancy wherein are seen retinal hemorrhages and epistaxis as in Solomons'<sup>9</sup> case. In this connection it is interesting to note the case reports of the following men: Shaw<sup>10</sup> reports a 39-year-old primipara with albuminuria who developed an immediate hematoma in a nontraumatic delivery which was not drained, with a fatal result; Gibberd<sup>11</sup> reports a case of a primipara with albuminuria who developed epistaxis and a hematoma ante partum which required drainage to permit delivery; and Danby,<sup>12</sup> Liepman,<sup>13</sup> Hirsch,<sup>14</sup> and Krause<sup>15</sup> also report cases of hematoma associated with albuminuria with or without hypertension.

There can be little doubt that trauma and pressure necrosis alone are not the only factors in the production of hematomas, as in too many cases the birth is spontaneous, not unduly prolonged and delivery is accomplished without any apparent trauma. Furthermore, if one can establish the presence of vascular changes in certain conditions in pregnancy which produce hemorrhagic tendencies in other tissues of the body, it is perfectly reasonable to assume that these vascular changes would produce hemorrhage in the pelvic tissues where the most bruising and stretching occurs.

Prior to the time of active treatment of these hematomas there was according to DeLee<sup>2</sup> and others a mortality rate as high as 40 per cent. However, for the last thirty years the mode of treatment recommended has been more or less active, and, during that time, the mortality statistics have been essentially the same, except in Williams'<sup>5</sup> report on 33 cases where the hematomas were retroperitoneal in type, in which series there was a mortality rate of 56 per cent. In Frank-Kamenetsky's<sup>1</sup> report there is a gross mortality of 9.5 per cent, a series of 82 cases. Vaux<sup>4</sup> reports a 12 per cent mortality, and in this series of cases there was a mortality rate of 8.3 per cent.

CASE 4.—Patient, multipara, aged 23 years, had a low forceps delivery, with episiotomy and repair at her first delivery. The present delivery was spontaneous with episiotomy and repair. Four hours after delivery she had extreme pain which was completely unrelieved by opiates. There was a bluish, fluctuating tense mass in the region of the left labia about the size of a grapefruit, and the vaginal cavity was filled. Within another hour she was in shock, for which she received 2 blood transfusions of 500 c.c. each. When she recovered from her shock the hematoma was incised. About 2,500 c.c. of clots were evacuated and the cavity was packed. She was given another 500 c.c. blood transfusion about four hours later and had an uneventful convalescence. She has since delivered spontaneously with no difficulty.

CASE 5.—Patient, primipara, aged 19 years, had a posterior position which rotated and delivered spontaneously without laceration. Eight hours later she had severe pain and left labial edema with some discoloration. Ice packing and tight compresses were applied. Obstetric consultation was requested and the consulting obstetrician flatly refused to allow interference and continued the expectant treatment. The following day the patient had two severe chills with the temperature as high as 105° F. She continued to have chills several times a day, and two days later surgical consultation was obtained. The surgeon felt the infected hematoma mass would drain spontaneously and suggested further expectant treatment. On the sixth day a small draining sinus developed from which came a little serosanguineous material, but the main mass did not drain. Her sepsis continued and became progressively worse and she died on the twelfth day. Permission for an autopsy was not obtained.

CASE 6.—The patient was a multipara, aged 35 years. Breech extraction of a frank breech was performed with episiotomy and repair. She began complaining of pain on the eighth day and developed right labial edema on the ninth day. On the tenth day the tense, fluctuating vaginal mass was incised and about a pint of clots were removed, but she was not packed. The pain recurred and again on the thirteenth day the cavity was reinvaded, the clots evacuated, and the packing inserted and left in place for twenty-four hours. She ran a low grade temperature until the nineteenth day and left the hospital, well, on the twenty-second day.

CASE 7.—The patient, a primipara, aged 25 years, delivered spontaneously with episiotomy and repair. Three hours after delivery she developed severe perineal pain, the unilateral edema appeared in five hours, and seven hours after delivery the hematoma was incised, the clots evacuated and the cavity and vagina packed. The packing was removed in eighteen hours and she had an uneventful convalescence.

CASE 8.—The patient, a primipara, aged 30 years, was delivered by difficult mid-forceps and episiotomy with immediate repair. Within an hour she began to have severe pain and unilateral edema. In ten hours there was a large, swollen, tender fluctuating mass beneath the left labia majora with a bluish discoloration. This was incised, about a quart of clots were evacuated, and the cavity and vagina packed. Because of her anemia she was given 2 transfusions in the succeeding forty-eight hours, and although she ran a low grade temperature, she was well upon leaving the hospital on the nineteenth day.

CASE 9.—The patient, a primipara, aged 28 years, delivered spontaneously with second degree laceration and repair. Within nine hours she had developed a typical hematoma of left sublabial region which was incised; about 1,500 c.c. of clots were evacuated, and the cavity and vagina were packed. She was given 500 c.c. of blood. She ran a low grade temperature for eight days but following another 500 c.c. transfusion the temperature returned to normal and she left the hospital in good condition.

CASE 10.—The patient, a primipara, aged 23 years, delivered spontaneously without laceration. Within two hours a large hematoma had developed in the right labia majora, which upon incision yielded 1,250 c.c. of measured clots. The cavity and vagina were packed, and she was given 750 c.c. of blood. She had an uneventful convalescence.

TABLE I. PARITY

	NUMBER OF CASES	PRIMIPARAS		MULTIPARAS	
		NUMBER	PER CENT	NUMBER	PER CENT
Our series	12	10	83	2	17
Total series	127	74	59	53	41

TABLE II. TYPE OF DELIVERY

	NUMBER OF CASES	SPONTANEOUS		OPERATIVE	
		NUMBER	PER CENT	NUMBER	PER CENT
Our series	12	9	75	3	25
Total series	127	73	58	54	42

TABLE III. TYPE OF HEMATOMA

	NUMBER OF CASES	IMMEDIATE		DELAYED	
		NUMBER	PER CENT	NUMBER	PER CENT
Our series	12	11	91	1	9
Total series	127	110	87	17	13

TABLE IV. MORTALITY RATE

	NUMBER OF CASES	NUMBER OF DEATHS	PER CENT
Our series	12	1	9
Total series	127	27	21

It would appear that if this complication is early recognized and actively treated the mortality rate can be materially improved. Another interesting observation is that in our series of cases handled in this manner, on subsequent examination there was practically no residual distortion of tissue, and three of this series have subsequently delivered with no pathology referable to their previous complication.

## CASE REPORTS

CASE 1.—Patient, primipara, aged 25 years, three-weeks premature, no albuminuria, no hypertension, had a spontaneous delivery and an episiotomy with immediate repair. Eight hours after delivery edema of the labia was observed and the patient was suffering from severe perineal pain. The hematoma was incised, the clots were removed, and the cavity was packed. There was an uneventful convalescence.

CASE 2.—Patient, primipara, aged 28 years, had a three-weeks premature delivery due to induction of labor for albuminuria and hypertension. There was a spontaneous delivery of a small fetus with episiotomy and immediate repair. Within two hours the patient was having severe pain, edema of the left labia, and there was a typical hematoma mass. It was incised, the clots were removed, and it was left unpacked. There was some drainage for eight days, but the patient left the hospital in good condition.

CASE 3.—Patient, a primipara, aged 27 years, had a spontaneous delivery with episiotomy and repair. Two hours after delivery the patient had severe pain which became progressively worse, and she developed edema of the left labia. Vaginal examination revealed a tense, painful, fluctuating mass filling the vagina from the left and arising high in the vagina. It was incised, the clots were evacuated, and the cavity was packed. The patient made an uneventful recovery.



Another case with subperitoneal hemorrhage occurred last spring at the Greeley Hospital, a town about fifty miles from Denver, and was attended by Dr. N. A. Madler who consulted me about five hours after the occurrence of the initial signs. I did not see the patient but will report the case, because it is typical of an extensive retroperitoneal hematoma.

A woman, aged 21 years, para ii, was delivered normally with no medication and an easy labor. About two and one-half hours afterwards, she complained of abdominal pain and was later in shock. A mass was seen in the vagina, and there was a rising upwards of the fundus almost to the xiphoid. There was very little external bleeding. She was given morphine and intravenous glucose. Twelve hours later she was in profound shock, clammy, the temperature subnormal, and the pulse 160. An extravasation of blood around the anus and perineum with discoloration into either buttock was present. The cervix could not be felt, due to the large mass filling the vagina pressing forward from behind.

After transfusion an incision was made through the posterior vaginal wall with the evacuation of large clots. This was followed by active bleeding which could not be controlled with packs, and necessitated a laparotomy.

On opening the abdomen the uterus was found lifted up by a large subperitoneal hemorrhage; there was bloodstained fluid but no intraperitoneal bleeding. A hysterectomy was done. Extravasation had occurred into both broad ligaments, separating the leaves, and extended upwards along the sigmoid and downward along the rectum. The starting point of the bleeding could not be determined. With the exception of a severe reaction following one of several transfusions, this patient made a good recovery.

DR. J. R. MANLEY, DULUTH, MINN.—I would like to report two cases with this condition. (1) The first was a primipara who delivered spontaneously with a small first degree laceration. Some time later she went into shock, experienced considerable pain and something was coming out of the vulva which had the appearance of a placenta. It was a hematoma of the vaginal wall, about the size of a grapefruit, and had the appearance of the fetal side of the placenta. The patient was taken to the operating room and the hematoma opened. The hematoma did not extend up under the peritoneum, and there was very little difficulty in stopping the bleeding.

(2) The second case was not recognized for about a week. She had had a spontaneous delivery, followed by thrombotic hemorrhoids and a constant complaint of pain around the perineum. I finally decided to remove the hemorrhoids before she left the hospital, and only then discovered a large hematoma of the vulva.

DR. WILLIAM H. RUBOVITS, CHICAGO, ILL.—My case, a woman, seen in Michael Reese Hospital, began to bleed from the upper end of the episiotomy incision about the eighth day following delivery. In the course of the next eight weeks she was packed at least every other day. The wound was resutured ten times. She was given 10 transfusions. The internal iliac arteries were ligated, and the woman recovered. A detailed study of the blood by a competent hematologist revealed no dyscrasia of any kind. Nevertheless about two and one-half months after leaving the hospital, this patient began to bleed from the base of the tongue following a violent kiss, and died from this hemorrhage.

DR. HAMILTON (closing).—We were unable to demonstrate the direct arterial bleeding in any of our series.

I was interested to hear Dr. Rubovits' remarks because I felt that many of these cases were based on a hemorrhagic tendency. I think the cause in the beginning is a very small artery, but the additional bleeding is probably venous in origin, at least it would appear so from the inspection of the cavity. The difficulty, as has been mentioned, is in trying to find the offending vessel.

CASE 11.—The patient, a primipara, aged 37 years, delivered spontaneously with episiotomy and repair. Three hours later she developed severe pain in the left labia along with unilateral labial edema. Vaginal examination revealed a rounded, tense, fluctuating, painful mass, arising high in the vault of the vagina. This was incised, about 400 c.c. of clots were evacuated, and the cavity and vagina were packed, with the packing being removed in twelve hours. She had an uneventful convalescence.

CASE 12.—The patient was a primipara, aged 19 years. Labor was induced at thirty-seven weeks' gestation for albuminuria and generalized edema without hypertension. About four hours prior to delivery she had severe epistaxis. Delivery was spontaneous without laceration. About four hours after delivery she complained of severe pain in the left side of the perineum, and a very marked edema of the left labia was found. Vaginal examination revealed a mass the size of an orange protruding in the vaginal cavity from the left. This was incised, about 600 c.c. of clots were evacuated, and the cavity and vagina were packed. The packing was removed in fourteen hours and, aside from another attack of epistaxis the following day, she had an uneventful convalescence.

I wish to express my deep appreciation to Drs. J. G. Webster, Paul V. O'Rourke, Buford G. Hamilton, Ralph R. Wilson, and E. C. White for allowing me to draw upon their private records in compiling the cases included in this report.

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1107 BRYANT BUILDING

#### DISCUSSION

DR. CLARENCE B. INGRAHAM, DENVER, COLO.—We have had but one case of vulval hematoma at the Colorado General Hospital. A twenty-seven-year-old woman, who had had one previous pregnancy, delivered elsewhere by cesarean section at seven and one-half months because of a kidney complication, was admitted to our institution in the last month of her second pregnancy with a blood pressure of 150/100 and a right-sided hydronephrosis. Labor occurred at term. There was a spontaneous premature rupture of the membranes; the first stage lasted twelve hours and was without medication. When the head was well engaged and the cervix fully dilated, a hematoma of the left labium majus began to form, reaching within an hour a diameter of about three and one-half inches and encroaching upon the vagina sufficiently to interfere with progress. Forceps were applied, with an easy delivery of a 3,200 Gm. child in right occiput anterior. During this procedure the hematoma ruptured at the junction of the labium and vagina with the escape of clots and a large amount of bleeding which was controlled by pressure. Her convalescence was uneventful except for four days of moderate temperature, less than 101° F.

Among these 100 cases, there was one set of twins, 1 breech delivery, and 4 patients were induced medically at term. All deliveries were spontaneous.

The average age of the patients was 31 years, the youngest being 20 and the oldest 45 years of age. Average parity was  $5\frac{1}{2}$ . The average period of post-operative hospitalization was 9.4 days, the average length of labor being 8.75 hours. The longest labor was twenty-four hours and the shortest, one and one-half hours. The average time from rupturing of the membranes to delivery was two hours.

#### MORBIDITY AND MORTALITY

There was no mortality in the 100 charity patients, and the morbidity was 2 per cent, or 2 cases, using the standard of morbidity as approved by the American Committee on Maternal Welfare. One patient developed pyelocystitis and ran a fever from  $99^{\circ}$  to  $103^{\circ}$  F. for five days. On the sixth day the temperature was normal. She was treated with sulfanilamide and given two blood transfusions. Otherwise she made an uneventful recovery. The other developed puerperal sepsis, temperature beginning on the third day and ranging from  $100^{\circ}$  to  $104^{\circ}$  F. for one week. She was treated with sulfanilamide and blood transfusions. Otherwise she made an uneventful recovery. One patient had a temperature of  $101^{\circ}$  F. on the fourth post-partum day only and ran an afebrile course during the puerperium. One patient had a chill on the first post-partum day and a temperature of  $102^{\circ}$  F., and then ran an afebrile course during the puerperium. We had four minor wound infections in the patients who had syphilis. The drainage was mostly serum and not pus, but all wounds healed before the patients left the hospital.

#### TECHNIQUE OF OPERATION

All of the patients were selected from those who had had spontaneous deliveries and no contraindications to operation. Immediately following delivery the patient was given  $\frac{1}{4}$  gr. of morphine and  $\frac{1}{150}$  gr. of atropine. The abdomen was prepared for operation and the patient sent to the operating room one hour after delivery. In about one-half of the cases we used cyclopropane-gas-anesthesia and in the other one-half we used ether. An incision  $1\frac{1}{2}$  inches long was made immediately below the umbilicus, and the uterus was pushed to one side, bringing the tube into the incision. The tubes were picked up about the middle third and a large loop was crushed in three places. Each crushed place was tied with a linen suture inserted through the mesosalpinx. This is somewhat different from the Madlener technique: where a small loop is used and crushed in three places but tied in two. The postoperative orders are the same as our routine post-partum orders, that is giving a regular diet and enema on the third day, and rarely, if ever, do the patients require any opiates other than codeine and aspirin for afterpains.

#### FOLLOW-UP

To date, we have not had any pregnancies occur after our triple ligation method. All of the patients have been highly pleased to date with the results of the operation.

We had three patients who complained of mild dysmenorrhea following the operation, who had never had any discomfort during menstruation before. There were four patients who menstruated every two weeks after the menses returned following operation, who did not receive any treatment and adjusted themselves to a twenty-eight- to thirty-day cycle.

#### DISCUSSION

This report of 100 patients sterilized one hour after delivery was done to determine the safety and advisability of post-partum sterilization. Our results compare very favorably with those reported by

## POST-PARTUM STERILIZATION\*

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*(From the Department of Obstetrics of the Baroness Erlanger Hospital)*

DURING the last fourteen months at the Baroness Erlanger Hospital, we have sterilized one hundred women on the charity service by tubal ligation, within an hour after delivery. Other than reports made by Dr. Skajaa of Switzerland and in March of this year by Drs. Adair and Brown of Chicago, we have no statistics for comparison with our results.

As there are 26 methods by which the female may be sterilized, this seems to prove that no one method is ideal. For example, the senior author (H. P. H.) has seen one patient who had never been pregnant prior to an operation, at which both tubes and the right ovary were removed and the left ovary which was cystic was resected, and then sutured to the fundus of the uterus. Eight months after the operation, this patient became pregnant and has delivered three full-term infants since then.

Many of the articles written on sterilization deal with women past the childbearing age. Our group is composed entirely of mothers in the childbearing age, and sterilization was performed following only spontaneous deliveries.

### LEGAL CONSIDERATION

Since there is no special law dealing with sterilization in Tennessee, we follow the procedure of having two physicians state that it is to the best interest of the mother's health that she should be sterilized. A slip is signed by the patient and her husband giving permission for sterilization, and at the time of the operation we have the chief of the prenatal clinic with the attending man on the indoor service to sign the prenatal record, recommending post-partum sterilization.

TABLE I. INDICATIONS

Of the 100 charity patients, 90 were white and 10 colored.	
Hypertension	1
Recurrent pyelitis	1
Toxemia of pregnancy	1
Nephritic toxemias and hypertension	1
Syphilis	10
Social and economic	30
Pulmonary tuberculosis	4
Rheumatic heart disease	2
Multiple pregnancies	50

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report further on post-partum sterilization and compare the results with charity and private patients.

### CONCLUSIONS

1. One hundred cases of tubal ligation done one hour after delivery on patients who delivered spontaneously are reported.
2. There was no mortality in the 100 cases reported. We had a 2 per cent morbidity.
3. Our percentage of cesarean sections have materially decreased since doing post-partum sterilization.
4. To date we have not had any failures reported.
5. Post-partum sterilization offers an economical means of sterilization from the standpoint of hospitalization, as it does not prolong the stay in the hospital and does not give the patient any discomfort as does the average pelvic operation.
6. The time consumed in the operation is short, averaging fifteen minutes.
7. We feel that one hour after delivery is the best time for it to be done, because the fundus is even with the umbilicus and we have less difficulty in exposing the tubes than we would if we waited a few days longer.
8. If the uterus is not manipulated too much, the bleeding during the operation will be small.
9. Involution of the uterus was not retarded.
10. We feel that post-partum sterilization is safe in selected cases.

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### DISCUSSION

DR. CECIL W. SEIBERT, WATERLOO, IOWA.—Any one who practices obstetrics will have from time to time patients who have definite indications for sterilization. It is extremely difficult to get these patients back in the hospital at a later time for the operation. This is not only a financial burden which is in many cases prohibitive, but most mothers are loath to leave their young baby in the care of strangers until after it is a year old, and by that time another pregnancy may be present. The procedure that has just been recommended escapes these disadvantages and will appeal to most patients as being both logical and practical.

I believe that the small incision should be emphasized. This should not be an exploratory operation, and with a small incision, there is no temptation to remove the appendix or resect cystic ovaries, etc. The Madlener technique which is now quite generally used lends itself well to the small incision. Tubal or cornual resection is at times somewhat bloody, and many cases of pregnancies following sterilization by this technique have been reported.

In the past year I have had occasion to do five post-partum sterilizations in private practice. These have all been done on the third post-partum day; the thought being that any serious degree of puerperal sepsis should manifest itself by that time, in which event the operation would not be done. There was no morbidity and all were discharged on the tenth post-partum day.

DR. FRED L. ADAIR, CHICAGO, ILL.—This operation is one that can be done very simply, exposing first one tube and then the other, clamping and ligating each, and it can be done under local anesthesia. I believe it is a safe operation

Adair and Brown. They reported a series of 50 cases with a morbidity of 12 per cent, and our morbidity was 2 per cent. In neither series was there any mortality. The average stay in the hospital of our patients was 9.4 days, and theirs was 11.3 days. Our average parity was 5.5 and theirs was 4.6. We did one-half of our operations with ether and one-half with cyclopropane-gas. The patient who developed pyelocystitis received gas, and the patient who developed puerperal sepsis was given ether. Adair and Brown used local anesthesia. Dr. Skajaa stated that using ether for anesthesia increases chances for thrombosis and embolism, which did not occur in our series. Labor was induced medically in 4 per cent of our patients, compared to Adair and Brown's 10 per cent. We must admit that we were very lenient in our indications for sterilization. In a majority of the cases under the headings, "social and economic and multiple pregnancies," we were influenced by their mentality in being able to control future pregnancies. In patients who we considered had intelligence to use the accepted method of contraceptive procedure, we did not urge sterilization. We were very cautious in selecting the patients who did not have any difficulty at delivery and no chances of infection. Thereby, we refused all patients for post-partum sterilization who had had an operative delivery of any kind. In most of our patients the operation was done by the resident surgeon of the hospital, and we insisted that in ligating the tubes the operator must follow the tube out to the fimbriated end to be sure that he was ligating the Fallopian tube and not the round ligament. We feel that the triple ligation gives an added percentage of safety over double ligation. We have not included any cases of tubal ligation where the patient had indication for cesarean section. We know definitely that we have not done as many cesarean sections since we have been doing post-partum sterilization as we did formerly with sterilization as an indication. We feel that any individual who has had all the children she desires, and is past thirty-five years of age should be sterilized according to her wishes. Previous reports on tubal ligation show that there is a 5 per cent failure over a period of ten years, so the nearer the menopause the patient is the smaller will be the percentage of failures.

Since the above report is so favorable, we would like to sound a note of warning by giving the results obtained in 25 private cases which have been done at the Erlanger Hospital in the past eighteen months. In this group there was one failure after ten months, and there was one death twelve days post partum due to embolus. This patient weighed 300 pounds, had a blood pressure of 240/130, and delivered a macerated fetus at term. She had a chronic nephritis and was given an ether anesthetic. She had a low grade infection following delivery and operation which lasted a week. Her temperature never went above 102° F. On the twelfth day when she started to get out of bed she died suddenly due to embolus. The patient having hypertension, chronic nephritis, and delivering a macerated fetus, probably should not have been sterilized. At a later date I hope to

after extraction to exhaustion as recommended by Thompson.<sup>6</sup> Beginning with smaller amounts, it was determined that a dose equivalent to 12 gr. (0.8 Gm.) U.S.P. ergota preparata, administered by mouth at intervals of from two to three hours, was effective for inducing labor.

Castor oil, from one to two ounces, was given one-half hour before the first dose of ergot. Usually two, but occasionally three doses of ergot have been given and labor has been considered induced if uterine contractions commenced within twenty-four hours after the administration of the first dose. If, as has happened on a few occasions, pains began after the ingestion of the first dose of ergot, no more was given.

U.S.P. ergota preparata is defatted and is standardized to possess the equivalent of 0.5 mg. of ergotoxin ethanesulphonate each gram. If kept dry, the product is stable indefinitely. According to Thompson,<sup>7</sup> all of the alkaloids in ergot except ergonovine may for practical purposes be calculated as ergotoxin. The U.S.P. assay then, while adequate for all of the other component alkaloids of ergot, is inadequate for the determination of the ergonovine equivalent content. Theoretical objection to whole ergot for oxytocic usage is possible on the grounds that a high ergotoxin equivalent assay may be accompanied by a low ergonovine content or vice versa. However, a number of workers<sup>8, 9</sup> have shown that the total alkaloid to ergonovine relationship in various samples of whole ergot is from 4 to 5 to 1. Whole ergot, therefore, may reasonably be expected to contain as ergonovine 20 to 25 per cent of the whole alkaloid content. The 12 gr. equivalent of the ergot used during these observations was actually 165 mg. which, on a basis of the above computation, would contain from 0.07 ( $\frac{1}{1400}$  gr.) to 0.1 ( $\frac{1}{1000}$  gr.) mg. of ergonovine equivalent strength.

The results of our observations in tabulated form are given in Tables I and II.

TABLE I. ATTEMPTED ERGOT INDUCTIONS

Group 1.	Ergot and castor oil	142
Group 2.	Ergot and castor oil plus posterior pituitary extracts	25
Group 3.	Ergot and artificial rupture of membranes, either before or after	26
Group 4.	Ergot and insertion of bougies	2
Total		195

*Fetal Mortalities.*—CASE 1.—Induced thirty days before term and two weeks after clinical and x-ray diagnosis of intrauterine death of the fetus.

CASE 2.—Difficult version and extraction, 9½ pounds, eighteen days post-mature baby, and thirty-six hours after induction with castor oil and ergot, 2 doses, with four-hour rest period intervening. Autopsy demonstrated intracranial hemorrhage. Primiparous mother.

CASE 3.—Outlet forceps, seventeen and one-half hours after induction with castor oil and ergot, 2 doses, and normally progressing labor. Infant made respiratory attempts but could not be resuscitated. No autopsy. Para ii mother.

*Fetal Morbidity.*—In the 184 pregnancies reported, all of which were from private practice, the babies have been observed during their hospital residence and in most cases afterwards by competent pediatricists. In the 181 living babies there has been no serious or unusual morbidity in the hospital, or as far as can be ascertained, during the afterlife.

*Maternal Morbidity.*—The maternal morbidity has been considered from the immediate and remote standpoint. Labor following the ergot method of induction generally has not been more rapid than that in spontaneous labor. In Group I of the tabulated results, there were 58 primiparas and 53 multiparas. The shortest labor in

if the conditions are carefully evaluated. It is very important to eliminate cases that have been manipulated or that are what we might call potentially infected.

One point of view we have is somewhat different from that taken by Dr. Seibert. He feels that he should wait until the possibility of puerperal infection is excluded. On the other hand, we take the point of view that the genital tract becomes more or less infected or contaminated by bacterial growth, the longer you wait following delivery. We have placed a twenty-four-hour limit on puerperal sterilization and would be rather inclined to follow an even more limited period of time than to extend it beyond the twenty-four-hour limit. I believe this is very important in connection with the management of these cases, because the lochial discharge does change following delivery. Any case that is mechanically induced, as distinguished from medical induction, should be excluded from the series, as well as any case of operative delivery by version or extraction, as pathogenic microorganisms may be present and might become active in the vicinity of the tube. This type of case is not really suitable for vaginal sterilization, so I presume that Dr. Hewitt would not advise that within the twenty-four-hour limit after delivery.

DR. P. B. RUSSELL, JR., MEMPHIS, TENN.—We agree with Dr. Adair that within twenty-four hours this is a simple procedure without much risk. Some of our staff have used the Madlener technique, others have used the method suggested at one time by the late Dr. Williams, but the success of the ligation depends upon the operator. Fistulas will result if the tube is crushed too gingerly, or the sutures cut through.

DR. HEWITT (closing).—About the time of operation, we do it within one hour because that is the safest time up to twenty-four hours. We have had some which were done as late as sixteen hours. Our results show that it is safe to do post-partum sterilization by tubal ligation.

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## THE INDUCTION OF LABOR WITH SMALL DOSES OF POWDERED ERGOT\*

### A PRELIMINARY REPORT

CLAUDE J. EHRENBERG, M.D., OWEN F. ROBBINS, M.D., AND  
JOHN A. HAUGEN, M.D., MINNEAPOLIS, MINN.

THE observations from which this preliminary report is made began in 1935, following a dramatic maternal and fetal death ten hours after the first ingestion of three 5-gr. doses of quinine sulphate. Although the cause of death was not proved by an autopsy, the circumstances were such as to permit of no other conclusion than fatal quinine poisoning.

A growing literature reveals the dangers of quinine for the prospective mother and the fetus, the appreciation of which is indicated by the general recession from the use of quinine for the purpose of labor induction.<sup>1-4</sup> Contrary to obstetric opinion, we have found that small doses of ergot can be tolerated by the pregnant woman without ill effect. This special ergot is in dried powdered form and has been standardized according to the *United States Pharmacopoeia*, No. XI,<sup>5</sup>

\*Presented at a meeting of the Central Association of Obstetricians and Gynecologists, Kansas City, November 2 to 4, 1939.



The condition of the cervix uteri at the postnatal interval examination has been used as an index of the remote morbidity. While it is impractical to describe in detail each case, the result of ergot induction on the late post-partum condition of the cervix has not been conducive to greater cervical pathology than in spontaneous labors. No third degree, a few second degree, and a number of first degree lacerations of the cervix were observed.

While the group of toxemia patients in this series is too small to be of statistical significance, a few observations may be worth noting. The blood pressure readings taken at fifteen-minute intervals, after the ingestion of ergot, revealed no elevation in the systolic and diastolic readings during a three-hour period. Although no definite water balance studies were made, the averages of the twenty-four-hour fluid intakes and outputs for the first two days post partum, in a group of patients induced with ergot, were no different than the averages in a group of patients in whom no ergot was used. The patients with toxemias had no greater uterine response to ergot than those without toxemia. This was observed carefully because of the known increase in uterine irritability of the toxemia patient to pituitrin administration.

Because of the above observations, and because of the high percentage of induced labors in this small series, the method would seem to be of distinct value in the toxemia patient, in which as Holman and Mathieu<sup>10</sup> have pointed out, the need for labor induction is the greatest.

#### DISCUSSION

Recognized medical opinion traditionally has condemned the use of ergot before or during labor; a condemnation justified by a review of the history of this use of the drug. On the other hand, a more critical review may indicate that the difficulties arose not so much from the use of ergot as from the various methods of preparation which allowed rapid deterioration or which lacked proper standardization. Criticism of the methods of standardization of ergot does not properly belong in this report. However, since the isolation of the alkaloid ergonovine, a combination of standardizations is sufficiently possible and practical to demand a reconsideration of the oxytocic values of ergot before and during labor. This is especially true if the use of posterior pituitary extracts continues in its general relationship to labor induction and stimulation as at present. Pituitrin as shown by Adair and others,<sup>11</sup> Hofbauer,<sup>12</sup> and others, adds serious elements of danger if used for the induction of labor in the toxemia patient. Briefly, this danger lies in the pressor and the antidiuretic actions of pituitrin and because of the increased sensitivity of the pregnant toxemia uterus to pituitrin stimulation. The desirability of oxytocic stimulation for induction of labor in the toxemia patient may be found in ergot which is free from the above-named disadvantages.

The choice of the whole ergot or the alkaloid ergonovine as the therapeutic agent is also an unsettled question. Ergonovine has been accepted as containing most of the oxytocic principle of ergot, but this oxytocic principle may be augmented or detracted from in desirability when used in combination with the other components of whole ergot. More pharmacologic evidence is needed to determine whether the components of ergot act as synergists, antagonists, or purely in an additive manner. Burn<sup>13</sup> maintains that the oxytocic action of ergonovine is prolonged by the remainder of the com-

TABLE II. RESULTS

Ergot and castor oil	Group 1.		
Successful (39 days before to 24 days after term)	111	78.2%	
Failures (24 days before to 18 days after term)	31	21.8%	
Ergot and castor oil and posterior pituitary extracts	Group 2.		Groups 1 & 2.
Successful (8 days before to 17 days after term)	17	68.0%	76.0%
Failures (6 days before to 14 days after term)	8	32.0%	24.0%
Results in toxemia patients	17		
All received ergot and castor oil only			
Successful			
At term	6		
Past term (both seven days	2		
Before term (6 to 38 days)	8		
	16	(94%)	
Failures (26 days before term)	1	(6%)	
Ergot and artificial rupture of membranes (including 2 cases of toxemia)	26		
Shortest latent period	40 minutes		
Longest period (2 cases)	24 hours		
Average latent period—4 hours, 45 min.			
Cases varied 36 days before to 18 days after term			
Ergot and bougie insertion	2		
1 case latent period, 45 minutes (18 days after term)			
1 case latent period, 3 hours, 15 min. (14 days before term, toxemia)			
Total inductions using ergot	195		
Maternal Mortality	0		
Fetal mortality	3		

the primiparous group was four hours and the longest labor was thirty-six hours, the average being thirteen and one-half hours. In the multiparous group the shortest labor, excluding the case of intrauterine death of the fetus, was two hours and the longest labor was twenty-six hours, with the average being seven hours. Earlier, when the doses of ergot were given at shorter intervals, some patients experienced long pains, and some mild tetanic contractions were observed. However, these subsided in a few minutes and did not differ materially from the same condition observed on occasions when pituitrin has been used for the induction or stimulation of labor.

In one case in which partial placenta previa had not been recognized and in which labor was induced eighteen days past term, a vaginal hemorrhage of about 500 c.c. occurred seven hours after the second dose of ergot had been given. However, four, 2 minim doses of pituitrin, and two, 3 minim doses of thymophysin had been administered at intervals of one-half hour, immediately preceding the hemorrhage. At the time of the hemorrhage the cervix was 2 cm. dilated and about 40 per cent effaced. Cesarean section was performed immediately with a living baby and an uneventful convalescence for the mother.

Post-partum hemorrhage has not occurred in this series of cases.

The immediate repair of a lacerated cervix was done in 7 patients of the entire group. The incidence of subinvolution of the uterus and puerperal pyelitis was no more frequent than in a comparable group following spontaneous labor. There was one case of thrombophlebitis in the series, which occurred in the toxemia patient induced with bougies and ergot.

In my private practice, the incidence of syphilis is 1 per cent. You justly say to me that I should run routine Wassermann tests to catch the one in one hundred cases. If I am to play as safely as that with syphilis, can I be as safe with the use of ergot in the induction of labor? If safety applies in the one condition, it should apply in all methods.

DR. FRED L. ADAIR, CHICAGO, ILL.—The question of the induction of labor really resolves itself into two points. I think all of us believe that there are certain cases that require induction of labor for the safety of the mother or baby. There are other cases which fall into quite a different group, that is a convenience group where you want to induce labor for the convenience of the patient or the physician. I am unalterably opposed to the induction of labor in the second type. I believe we have not recognized that labor begins before the onset of pain. There is a preparatory stage which precedes the actual onset of labor as characterized by labor pain. I believe the induction of labor prior to the completion of this introductory stage carries great danger.

About ergot, Dr. Davis and I and others have been interested in ergot for a number of years. We will agree with Dr. Ehrenberg as far as we have been able to determine that the oxytocic principle of ergot properly used has no deleterious effect on the blood pressure. It is difficult for me to understand why such a drug as powdered ergot, so variable in its potency, should be used to induce labor where we have a known oxytocic principle with exact dosage. It is the oxytocic principle we are concerned with in the induction of labor. Some ergot preparations contain no oxytocic principle and others possess a large amount. The method of standardization used by the Bureau of Standards is no indication of the amount of oxytocic principle ergot contains, because the oxytocic principle is not tested by the methods used in the Bureau, thus the amount of the oxytocic principle in different preparations may vary enormously. It seems to me if ergot is indicated in the induction of labor one must use a preparation whose oxytocic principle can be determined exactly.

DR. EHRENBURG (closing).—I cannot agree with Dr. Pendleton when he states that time has proved quinine a safe drug when used for the induction of labor, and the literature of the last few years will bear me out. His generalizations on the use of ergot are the old, time worn, familiar statements and are not pertinent to this report, in as much as he makes no differentiation as to the types of preparation of the ergot. One cannot discuss ergot without first qualifying the preparation of ergot being used as to stability, standardization, and ergonovine equivalent strength. Dr. Adair's criticism of the use of powdered ergot in place of the oxytocic principle of the drug may be justifiable. However, there is some indication that the whole ergot acts more favorably than the oxytocic principle alone. More work will be necessary to prove or disprove this hypothesis.

We have shown, with the ergot we used, the manner in which the oxytocic principle or ergonovine equivalent strength has been arrived at, and, although this varies by approximately 25 per cent, the variation is no greater than that allowed for various posterior pituitary extracts. The statistical material in this report is, we believe, worthy of reporting, but our real reason for presenting this report is because we feel that the use of ergot before and during labor should be revalued in view of the more accurate method of standardization made possible by the discovery of the oxytocic principle.

ponent alkaloids of ergot. Ergot and ergonovine therefore, may exhibit the same possibilities of therapeutic choice as other drugs from which the active principles have been isolated.

### CONCLUSIONS

1. Ergot has been used for the induction of labor on 195 occasions in 184 patients of whom 17 were toxemias of pregnancy.
2. There was no maternal mortality and no increase of maternal morbidity.
3. There were three fetal deaths, as described, and no increase of fetal morbidity.
4. Standardized powdered ergot\* is stable and with carefully selected dosages is safe and effective for the purpose of labor induction.

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### DISCUSSION

DR. GEORGE F. PENDLETON, KANSAS CITY, Mo.—This paper stimulates two different emotions—caution and enthusiasm.

We induce labor either for the patient's benefit or for our own convenience. Moderate doses of castor oil and quinine can be safely used for this purpose in the normal woman. Neither drug will start uterine contractions before full gestation, unless there is an idiosyncrasy present. Neither drug is powerful enough in moderate doses to upset the normal physiology of labor. Time has proved this statement.

On the other hand, ergot is a more potent drug; it produces strong, prolonged contractions, and its action "hangs on." The effect is not a question of minutes but of hours.

Ergot stimulates all smooth muscles and especially those in the uterus and in the media coat of the arterioles. Is it safe to give ergot to the toxic patient and double the insult upon the already overirritated arterioles of that body? I believe that ergot is contraindicated.

The older doctors cautioned us that ergot given before the end of the third stage increased the number of retained placentas and disposed to contraction rings. They abandoned the use of ergot because of its profound, prolonged muscular action. Time has proved this statement by decreasing the number of cases of manual removal of placentas through small constriction "rings" of the so-called "difficult forceps" cases which, primarily, were often due to the latter.

The prolonged action of ergot brings up the question of increased intra-uterine pressure, which ergot should markedly increase. By its use do we eliminate safety to gain speed?

The action of ergot upon the arterioles of the uterus should not be forgotten. Coupled with the moderate ischemia produced by the normal labor contraction, may it not cause serious effects on the fetus? Is this safety for the baby?

\*The preparation used in these observations is in capsule form and was made by the Upsher Smith Co., Minneapolis, Minn.

death is relatively more common in the higher parities, when we take into consideration that 50 per cent of these cases occurred in women of para vi to para x.

The duration of gestation is revealed in Table II.

TABLE II

Weeks	28 to 31	32 to 35	36 to 39	40 to 43	Over 44	No record
Number	7	24	50	36	3	8

This table shows that while, as we would expect, the greatest number of babies died between the thirty-sixth and thirty-ninth weeks of gestation, approximately one-third of these babies were postmature, as judged by the standard method of estimating due date. This fact will be taken into consideration in discussing the prevention and treatment of this condition.

Since 30 of these patients were referred to us for delivery by an outside agency, no definite records were available. In 48 cases the fetal heart tones were still present at the last prenatal visit, so that in these 78 cases it was impossible to estimate the exact time that fetal death occurred. Although many of the latter 48 patients gave a history of not having felt fetal movements for a week or longer, this information was considered too inaccurate to be utilized in attempting to determine the length of time after death that the fetus was retained in the uterus. In the remaining 50 cases, the length of time the babies were retained in utero after the fetal heart tones were recorded as absent is shown in Table III.

TABLE III

Days	Less than 7	7-14	14-21	21-28	28-35	35-42	42-56
Cases	35	6	1	3	2	1	2

The great majority of these patients complained of no systemic manifestations directly attributable to the retention of a dead fetus in utero. A few patients did complain of nausea, anorexia, chills, and a bad taste in the mouth. Thus, the information gained from Table III is of extreme importance, since it shows that a dead fetus can be retained in the uterus for a period of time varying from one to 56 days, with no serious untoward effect on the mother.

The obstetric histories in these patients were studied to find out with what frequency intrauterine death of the fetus occurred in women who have had some other obstetric accident, as abortion or stillbirth.

TABLE IV. OBSTETRIC HISTORY

Abortions per patient	1	2	3	4	5	6	7	8
Number of cases	17	10	4	1	2	0	2	1
Stillbirths per patient	1	2	3	4	5	6	7	8
Number of cases	8	2	1	1	0	0	1	0

Table IV reveals the tendency for intrauterine death of the fetus to occur in women who give a history of repeated abortions or stillbirths.

As to the sex of the fetus, there were 81 males and 47 females in the entire series, a preponderance of males over females of two to one. The cases occurred equally as often in the white as in the colored races, despite the fact that approximately 33 per cent of our clinic cases are colored patients, indicating a much higher incidence of intrauterine fetal death in the colored patients.

Of the 79 patients registered with us and followed in our prenatal clinic, positive serology was obtained in 14, an incidence of 17 per cent.

Thus of the 69 cases in which the cause of the death of the fetus could be determined, we found that 45 of the deaths were due to some constitutional disease of the mother. The most important of these diseases were syphilis, late

# INTRAUTERINE DEATH OF THE FETUS AFTER THE TWENTY-EIGHTH WEEK\*

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(From the Service of the Chicago Maternity Center)

OUR purposes in investigating intranterine death of the fetus were: First, to ascertain as far as possible the most common etiologic factors producing this condition; second, to determine the mechanism by which death is produced; and third, to discover the best means of preventing this complication. Finally, by a critical analysis of our cases, we hoped to come to some definite conclusions regarding the most satisfactory method of managing this rather common complication, with the least possible harm to the mother.

The cases for this study were taken from the records of the Chicago Maternity Center, an out-patient clinic where practically all the confinements are conducted in the patients' homes. In the selection of these cases we utilized only those in which the fetus was known to have died after the twenty-eighth week of gestation, but before the onset of labor. In all, there were 128 cases conforming to this criterion. During the same period of time we had 16,834 deliveries; therefore, the incidence of occurrence of intrauterine fetal death was 1 in 131 cases, or 0.7 per cent.

The ages of the patients in this group varied from 15 to 44 years and were divided as follows:

15 to 19 years	10 cases
20 to 29 years	50 cases
30 to 39 years	60 cases
40 to 44 years	8 cases

From this it may be gathered that intrauterine death of the fetus is more likely to occur in women over thirty years of age, and more commonly in the third decade of life. This is of some slight significance when we realize that the average age of the patients in our clinic is 20 years.

In studying the distribution of cases according to parity, we find the situation as revealed in Table I.

TABLE I

Para	i	ii	iii	iv	v	vi	vii	viii	ix	x
No.	23	12	11	11	10	18	10	9	8	16

Thus, 23, or 17.9 per cent, were primiparas and 105, or 82.1 per cent, were multiparas. A review of our clinic records shows that 75 per cent of all our deliveries occur in women of para v or less, and the remaining 25 per cent in para vi or more. It then becomes readily apparent from an analysis of Table I that intrauterine fetal

\*Presented at the Eleventh Annual Meeting of the Central Association of Obstetricians and Gynecologists, Kansas City, Mo., November 2 to 4, 1939.

## RECOMMENDATIONS

All women who give a history of previous abortions or stillbirths should have a careful work-up, including routine serology, complete blood studies, and blood chemistry with particular reference to non-protein nitrogen retention and blood sugar. A basal metabolism test should be done and, if indicated, thyroid extract should be given throughout the duration of pregnancy.

Antisymphilitic therapy to be most effective must be started early and continued throughout the duration of pregnancy. The urine must be carefully examined for albumin and blood at frequent intervals throughout the course of treatment.

Diabetic patients should be under the joint supervision of an obstetrician and a competent internist. When a diabetic patient is pregnant and gives a history of having had one or more previous stillbirths, we should seriously consider terminating the case by a cesarean section about the thirty-eighth week of pregnancy. All other pregnant diabetic women who are well controlled and present no signs of cephalopelvic disproportion can be delivered from below.

Intrauterine death of the fetus *per se* calls for no active interference. In the absence of urgent maternal indications, labor should not be induced by either medical or mechanical means. Our specific objections to medical induction in this type of case are that it is quite often unsuccessful and, moreover, may actually expose the patient to danger by causing the membranes to rupture without immediately initiating labor. Our objections to all forms of mechanical inductions are the greatly increased dangers brought about by the introduction of virulent organisms from without. This is especially true when we realize that a uterus harboring a macerated fetus offers an excellent culture medium for bacterial growth. In conducting the actual labor, operative interference should only rarely be resorted to. These cases should be terminated with the least possible injury to the mother, therefore episiotomies should seldom if ever be done. If there is some complication, such as toxemia or intrapartum sepsis, that endangers the mother's life and operative interference is indicated, the procedure of choice is a mutilating operation, usually craniotomy.

## SUMMARY AND CONCLUSIONS

1. Intrauterine death of the fetus in our clinic occurred 128 times in 16,834 deliveries, an incidence of 0.7 per cent.

2. This complication occurs more frequently in women over thirty years of age.

3. Seventy per cent of our patients went into labor spontaneously within seven days after the known death of the fetus. The remaining 30 per cent did not go into labor for a period varying from seven to fifty-six days.

4. There is a marked tendency for this complication to occur in patients having a previous history of repeated abortions or stillbirths.

5. Despite the fact that fewer deliveries occurred in the para v to para x group, this group still accounts for 50 per cent of the total

TABLE V. CAUSE OF FETAL DEATH

MATERNAL CAUSES		FETAL CAUSES		UNKNOWN
Syphilis	18	Cord pathology	11	59
Late toxemias	12	Monsters	5	
Abruptio placentae	9	Polyhydramnios	2	
Diabetes	6	Volvulus and gangrene of the		
Intrapartum sepsis	2	bowel	1	
Urinary tract infections	1	Dubois' abscess of thyroid	1	
Bandl's ring	1			

toxemias of pregnancy, including chronic nephritis, and diabetes mellitus. In 20 other cases, the cause of death was directly attributable to fetal pathology. Inasmuch as practically all of these babies were in various stages of decomposition, with the exception of the two with abscess of the thyroid and gangrene of the bowel, autopsy was of no value in determining the cause of death of the fetus.

The onset of labor was spontaneous in 118, or 92.1 per cent, of the cases. Medical induction was resorted to in 9 cases, or 7.3 per cent. Eight of these inductions were done for coexisting severe toxemia of late pregnancy which did not respond to conservative management. Bag induction was resorted to in one case for a fulminating toxemia, associated with a complete abruptio of the placenta with a blood loss of 1,500 c.c.

The termination of labor was spontaneous in 111 cases, or 86.8 per cent, and operative measures were employed in the remaining 17 cases, or 13.2 per cent. The types of operations performed were: Low forceps, 1; craniotomy, 13; vaginal hysterotomy, 1; breech extraction, 1; and version followed by extraction, 1.

The duration of labor was from one to eighteen hours in 98 cases, over eighteen hours in 17 cases, and precipitate in 13 cases, where the baby was born before the arrival of the doctor. The average duration of labor for the entire series was eleven hours and forty-one minutes. There were no maternal deaths in this series. One hundred and sixteen of these women had an uneventful puerperium and were discharged on the tenth day. The other 12 cases were considered febrile, a morbidity rate of 9.3 per cent. A very brief analysis of these cases showed one case of severe post-partum pyelitis, one case that was terminated by Dührssen's incisions and craniotomy after a twenty-nine hour labor, one case of a transverse presentation and prolapse of the cord, for which podalic version was done, and an eight and one-half pound baby extracted. Uterine exploration revealed a rupture in the lower uterine segment, and a subtotal hysterectomy was performed. After a stormy convalescence, the patient recovered. One patient had irregular pains for three days, at the end of which time her temperature rose to 102° F. and her pulse to 140, associated with a foul vaginal discharge. She was delivered by vaginal hysterotomy and craniotomy. The next patient delivered spontaneously; after a febrile course for twenty-one days she had a delayed post-partum hemorrhage which was controlled by intravenous ergonovine. Retained secundines were expelled at this time and her temperature returned to normal. One patient had multiple fibroids which became extremely tender after delivery; under conservative management the infection was controlled. Another patient contracted mumps and ran a febrile course for a few days. The remaining six patients had mild intrauterine infections and recovered within fourteen to twenty-four days. We wish to mention at this time that although our apparent maternal morbidity was only 9.3 per cent, this by no means can be considered accurate, inasmuch as all these patients were delivered at home where temperature readings are recorded only once a day on the average patient, and usually in the morning. The twelve cases herein cited were those in which post-partum pathology was easily discernible.

Based on an estimated blood loss of 500 c.c. or more, post-partum hemorrhage occurred in seven cases or an incidence of 5.4 per cent. This was of considerable interest to us in view of the existing consensus of opinion that excessive bleeding rarely follows the birth of a macerated baby.



DR. W. A. RUCH, MEMPHIS, TENN.—I wonder if in their series the authors found any cases of torsion of the cord, for in the last year I have seen three cases, one in a primipara. All the women had normal courses and negative Wassermann reactions, but at about the seventh month there was a cessation of fetal life. After two weeks, two of these patients responded to medical induction, but the other one did not, and we used a bougie. In each one of these cases there was nothing abnormal about the fetus except a torsion of the cord about one inch from the baby's body.

DR. FRED L. ADAIR, CHICAGO, ILL.—Dr. Edith Potter in our clinic analyzed some of the ante-partum deaths with which she has come in contact during her pathologic work. We have had in all 207 ante-partum fetal deaths; 81 were at term, 102 premature and 24 previable. It is interesting that in this group no maternal complication was diagnosed in 44 per cent. The contributory factors as far as the mother was concerned were toxemia and hemorrhage in 44.4 per cent. In this particular group the incidence of syphilis was rather low, 2.9 per cent. We had more deaths due to cord entanglement, 5.3 per cent. In the miscellaneous group, which included hydramnios, cardiac disease, pernicious anemia and hyperthyroidism, the percentage of deaths was 3.4. The fetus was normal or macerated in 35.8 per cent and malformed in 8.2 per cent. The toxemic group ran 20.8 per cent with the convulsive type in 1.4 per cent. We had placental detachment in 11.1 per cent, placenta previa in 3.4 per cent, placental detachment with toxemia in 7.7 per cent.

Hydramnios and other conditions in the miscellaneous group made up a very small percentage, showing there were diverse causes that contributed to the ante-partum deaths, some preventable, others not preventable. It is the preventable group in which we are interested from the standpoint of saving lives. The other presents a scientific interest and is a matter of academic concern, such as a seriously malformed fetus which we cannot save and would not want to save if we could.

TABLE I. MATERNAL COMPLICATIONS ASSOCIATED WITH ANTE-PARTUM DEATH OF THE FETUS

	TERM		PRE-MATURE		PRE-VIABLE		TOTAL		PER-CENTAGE	
No maternal complications		32		46		13		91		44.0
Fetus normal or macerated	25		37		12		74		35.8	
Fetus malformed	1		9		1		17		8.2	
Toxemia and hemorrhage		34		48		10		92		44.4
Toxemia	15		20		8		43		20.8	
Eclampsia			3				3		1.4	
Abruptio placentae	13		8		2		23		11.1	
Placenta previa	3		4				7		3.4	
Abruptio placentae and toxemia	3		13				16		7.7	
Syphilis (only 3 infants diagnosed as syphilitic)		3		3				6		2.9
Cord entanglements		7		3		1		11		5.3
Miscellaneous		5		2				7		3.4
Hydramnios	3						3		1.4	
Cardiac			1				1		0.5	
Pernicious anemia			1				1		0.5	
Hyperthyroidism	2						2		1.0	
Total		81		102		24		207		100.0

DR. DAVID A. HORNER, CHICAGO, ILL.—The reported cases showed no symptoms attributable to the dead fetus itself. That I brought out several years ago and showed that it is contrary to what the textbooks teach. Such symptoms as

number of fetal deaths in this series, indicating an increased tendency for intrauterine death of the fetus to occur in the higher parities.

6. The most common causes for death of the fetus during pregnancy, where such causes could be ascertained, were syphilis, late toxemias of pregnancy, including chronic nephritis and diabetes.

7. Spontaneous onset of labor occurred in 92.1 per cent, and in 7.9 per cent labor was induced because of maternal complications.

8. Delivery occurred spontaneously in 86.8 per cent, and was terminated by operative means in 13.2 per cent. However, 13 of these operative cases were craniotomies, most of which were done for teaching purposes.

9. One hundred sixteen, or 90.7 per cent, of these patients had a normal uneventful convalescence.

10. There were no maternal deaths in this series.

11. We have unequivocally demonstrated that intranuterine death of the fetus, regardless of the period of retention in the uterus, produces no serious untoward effects on the mother, and if managed conservatively should be attended by no maternal mortality.

8 SOUTH MICHIGAN AVENUE

#### DISCUSSION

DR. J. C. LITZENBERG, MINNEAPOLIS, MINN.—The reduced birth rate in the United States calls for the conservation of as many as possible of the nearly 100,000 babies who are born dead. This has not only a medical significance to us who are responsible for the survival of the babies, but it has an economic value.

How to prevent these intrauterine deaths is most important. Few of the patients are subjected to treatment, but there are several things that may be done to save most of these babies or at least a large percentage. Take the 77,000 who die in utero in the United States. The figures given here were, I believe, 128 cases in one community, so if that percentage were allotted to every community, it would probably account for most of the intrauterine deaths. The figures are astounding, 77,000. How many of these babies can be saved? It is very evident if we fulfill our function as careful obstetricians that many of these babies can be saved.

Care in regard to certain conditions will result in the reduction in number of uterine stillbirths. The chief of these are:

1. *Syphilis*.—This emphasizes the necessity of having a Wassermann reaction and a clinical diagnosis of syphilis in all such women, if we are to detect syphilis in the pregnant woman. If all syphilitic pregnant women are treated continuously until they come to labor, most of these babies will be saved as seen in the authors' table.

2. *Toxemia*.—Many of these babies can be saved by judicious treatment of the toxemias of pregnancy.

3. *Diabetes*.—These women must be watched with particular care, because if they are neglected in their treatment, we will have many stillborn babies.

4. *Pyelitis*.—One of the most neglected of the causes is urinary tract infection.

DR. GEORGE KAMPERMAN, DETROIT, MICH.—Conservatism in the handling of women with dead fetuses must be emphasized. The essayists have noted that mechanical induction is often serious because the dead pregnancy is a fertile field for the growth of microorganisms. When we introduce a foreign body into the uterus we must remember a dead fetus is already a foreign body. If a foreign body in the uterus does not start labor, we will not help by adding another foreign body.

TABLE I. SIGNIFICANCE OF CHRONIC CERVICITIS

QUESTION	YES		NO	
	NO.	PER CENT	NO.	PER CENT
Chronic cervicitis may be the cause of dysmenorrhea	80	63	47	37
Chronic cervicitis may be the cause of dyspareunia	84	64	47	36
Chronic cervicitis may be the cause of urinary symptoms	83	65	43	35
Chronic cervicitis may be the cause of pelvic pain	114	87	17	13
Chronic cervicitis may be the cause of backache	118	89	14	11
Chronic cervicitis may be the cause of sterility	129	97	4	3
Is chronic cervicitis important as a precancerous lesion	80	61	50	39
Is chronic cervicitis of importance as a focus of infection	103	78	28	22

TABLE II. ETIOLOGY OF CHRONIC CERVICITIS

MOST IMPORTANT ETIOLOGIC FACTOR	NO.	PER CENT
Birth trauma	97	73
Nonspecific infections	26	19
Specific infections	11	8

TABLE IIIA. DIAGNOSIS OF CERVICITIS

	YES		NO	
	NO.	PER CENT	NO.	PER CENT
Are stained smears important in the study of chronic cervicitis	55	41	79	59

	ALL CASES		MOST CASES		FEW CASES	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Biopsy is indicated in chronic cervicitis	8	6	35	26	91	68

TABLE IIIB. DIAGNOSIS OF CERVICITIS

	GREAT VALUE		MODERATE VALUE		LITTLE VALUE	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Schiller test. Value in chronic cervicitis	9	7	52	38	74	55
Colposcope. Value in chronic cervicitis	5	4	31	28	75	68

that the Schiller test and colposcope added little to the investigation of this condition. It would seem, therefore, that, in general, gross inspection of the lesion was considered adequate to make the diagnosis and to decide on proper treatment.

It will be seen from Table IV that by far the most common form of treatment used is actual cautery. The next in order of frequency are the three operative procedures: Sturmdorf amputation, trachelorrhaphy, and conization, which occupy about comparable positions. Cautery with chemical agents occupied a position quite similar to these three procedures, and cautery under anesthesia is next in importance. The remainder are used much less frequently.

headache, bad taste in the mouth, and fever were absent in the essayists' series and also absent in the series I presented several years ago.

As to the things to do if babies have died in utero, the answer is, there is nothing to do. The patient usually makes the diagnosis herself if she is beyond the period of viability. She feels no active movements, reports that to the doctor, and he cannot hear the heart tones, which bears out the diagnosis of a dead baby which the mother has already made. The failure of the uterus and fetus to grow also indicates that the baby is dead, and no harm is produced by allowing the baby to remain until nature takes care of it.

About the baby that dies in the latter part of the period of gestation, from being beyond term—if there is such a thing as an over-term baby or an overdeveloped baby, the less we do about it the less trouble we get into. While the size of the baby is an indication of its being fully developed, the only quite safe thing we can do is what we were taught not to do, that is a quick cesarean section. The use of pituitrin and bags, rupturing the membranes only make a bad matter worse. Bad results invariably follow too much manipulation. It is much easier, quicker, cleaner, and safer, I believe, in the right hands to do a cesarean section.

DR. UDESKY (closing).—In answer to Dr. Ruch's question whether we had observed any case of torsion of the cord, our diagnosis of most of the cases of cord pathology was a forelying cord or a cord lying in front of the baby's head. In answer to his other question of how long we would advise any one to wait before inducing labor if the baby is dead, our policy is strictly one of nonintervention. In the absence of maternal indications we do not induce labor.

## CHRONIC CERVICITIS\*

### REPORT OF THE COMMITTEE ON CLINICAL AFFAIRS OF THE CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

THIS report is based on the questionnaire circulated by the Committee during 1939 to the total membership of the Association. Reference to specific numbers of patients treated and other features requiring careful review of records, with the exception of complications, were purposely avoided.

From Table I it will be seen that, in general, it is felt that chronic cervicitis is a lesion of considerable importance in relation to body functions outside the pelvic viscera, as well as being the cause of significant changes in the pelvis.

It will be noted that the replies to all of these questions indicate that a majority are of the opinion that chronic infection of the cervix can be the causative agent of many important symptoms. It is of interest to note, however, that chronic cervicitis is considered more important as a focus of infection than as an etiologic factor in cancer.

Opinion concerning etiology (Table II) indicates that birth trauma is considered by far the most important causal factor. The remainder of those replying indicated that nonspecific infections rate second and specific infections third. The other causes mentioned were of minor importance.

Questions relative to the investigation of cervicitis (Tables IIIA and B) revealed that the majority did not feel that smears were important and that biopsy was indicated in only a few cases. Most of the men were of the opinion

\*Presented at the Eleventh Annual Meeting of the Central Association of Obstetricians and Gynecologists, Kansas City, Co., November 2-4, 1939.

of complications is about the same. There is a higher incidence of hemorrhage and infection with conization, while the incidence of stenosis of the cervix following Sturmdorf operation is sufficiently high to almost equalize this.

In view of the large number of complications reported, it is of interest to study the opinion concerning contraindications to treatment (Table VII). It will

TABLE VII. CONTRAINDICATIONS TO TREATMENT OF CHRONIC CERVICITIS

PELVIC CONDITION	NO CONTRAINDICATION TO ANY TYPE OF TREATMENT		CONTRAINDICATION	
	NO.	PER CENT	NO.	PER CENT
Retroversion of the fundus uteri	108	80	27	20
Inactive infection of upper genital tract	91	68	44	32
Active infection of upper genital tract	4	3	131	97

be seen that retroversion which has been emphasized by many as a contraindication is regarded as insignificant by 80 per cent of those replying. The opinion concerning infection as a contraindication seems about what should be expected. The fact, however, that 97 per cent avoided treatment in active infection and yet 148 acute infections attributable to the treatment are reported, suggests that the method of diagnosis of infection of the upper genital tract or its activity may be lacking in efficiency.

An analysis of the types of treatment believed to be contraindicated in retroversion showed that chemical cautery, coagulation, and conization were most objectionable, while in infection, these plus the various surgical procedures, as trachelorrhaphy, Sturmdorf amputation, and Schroeder amputation, are mentioned most frequently.

#### SUMMARY

This questionnaire study suggests that cervicitis is generally regarded as a lesion which can be of importance to the individual, both locally and in relation to various systemic conditions. It would seem that gross inspection is the chief method of diagnosis and that the various special instruments and tests recommended in its study are regarded by most as of little value. The large number of complications reported, most of which occurred following cautery of various types, should prompt us to improve our methods of diagnosis and treatment of this very common condition.

The Committee is grateful to those members who cooperated in this study. The investigation has been interesting and profitable to us, and we hope that it may be of some value to the Association.

*Norman R. Kretzschmar, M.D.*

*L. M. Randall, M.D.*

*John Brewer, M.D.*

TABLE IV. USE OF VARIOUS FORMS OF TREATMENT FOR CHRONIC CERVICITIS

TREATMENT	YES		NO	
	NO.	PER CENT	NO.	PER CENT
Cautery	127	94	8	6
Sturmdorf amputation	77	57	58	43
Trachelorrhaphy	72	53	63	47
Conization	68	50	67	50
Chemical cautery	66	49	69	51
Cantery under anesthesia	54	40	81	60
Hysterectomy	39	29	96	71
Schroeder amputation	38	29	97	71
Antiseptics	36	27	99	73
Coagulation	34	25	101	75
Diathermy	10	7	125	93

The incidence of complications following treatment was surprisingly large. A total of 685 complications attributable to treatment were reported. Of these, 276, or 40 per cent, occurred following cautery of the cervix. The list of complications recorded and their frequency is shown in Table V.

TABLE V. COMPLICATIONS FOLLOWING TREATMENT OF CHRONIC CERVICITIS

COMPLICATION	NUMBER
Hemorrhage	259
Stenosis of cervix	208
Upper genital tract infection	148
Cancer	16
Pyometria	12
Endometriosis	10
Cystitis	6
Abortion	7
Phlebitis	3
Prolonged labor	2
Dysmenorrhea	2
Others (single cases)	12
Total	685

While the high incidence of complications following cautery is partially explained by the more frequent use of this procedure, the number of complications seemed out of proportion although no comparative figures were available. An analysis of the complications following cautery revealed that upper genital tract infection (81), hemorrhage (80), and stenosis (80) made up 87 per cent of this group. An analysis of the three chief complications, hemorrhage, stenosis, and infection, revealed that cautery was responsible in 35 per cent, 38 per cent, and 54 per cent, respectively.

Since there has been considerable discussion concerning the relative merits of conization and Sturmdorf amputation, a comparison of complications following these was thought desirable (Table VI). It will be noted that the total number

TABLE VI. COMPLICATIONS FOLLOWING CONIZATION AND STURMDORF AMPUTATION FOR CHRONIC CERVICITIS

COMPLICATION	CONIZATION	STURMDORF
Hemorrhage	60	38
Stenosis of cervix	13	35
Upper genital tract infection	13	6
Others	8	7
Total	94	86

In further tables we wish to show the influence of other factors on mortality. According to Breese, "unless the weight factor is eliminated, effect of other factors influencing mortality is likely to be obscured, because of the very marked correlation between weight and mortality." We have attempted to eliminate this by the method described by this author, as follows: "using the mortality in each weight class of the entire group as a base line, we obtained the expected mortality for each factor as follows: the number of cases in each weight class is multiplied by

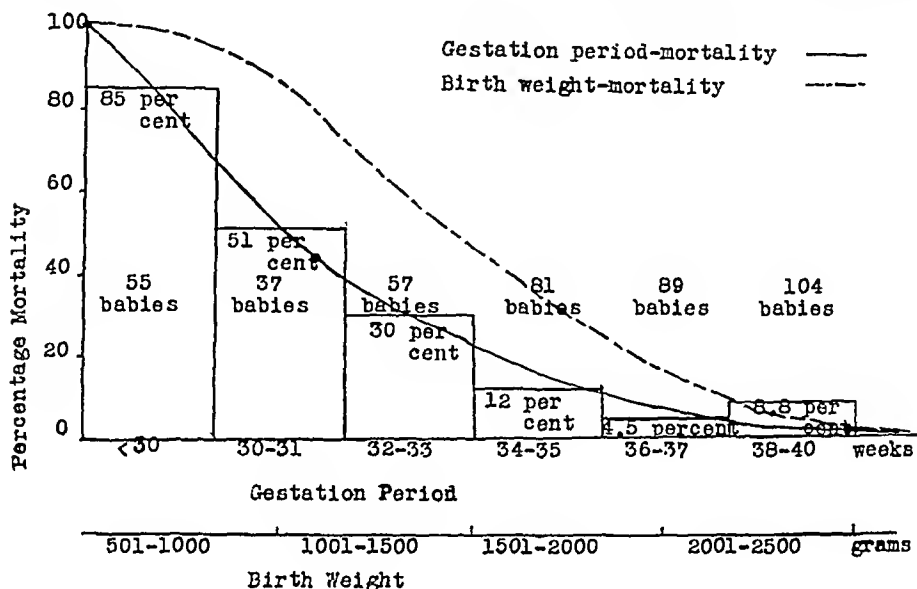


Fig. 1.

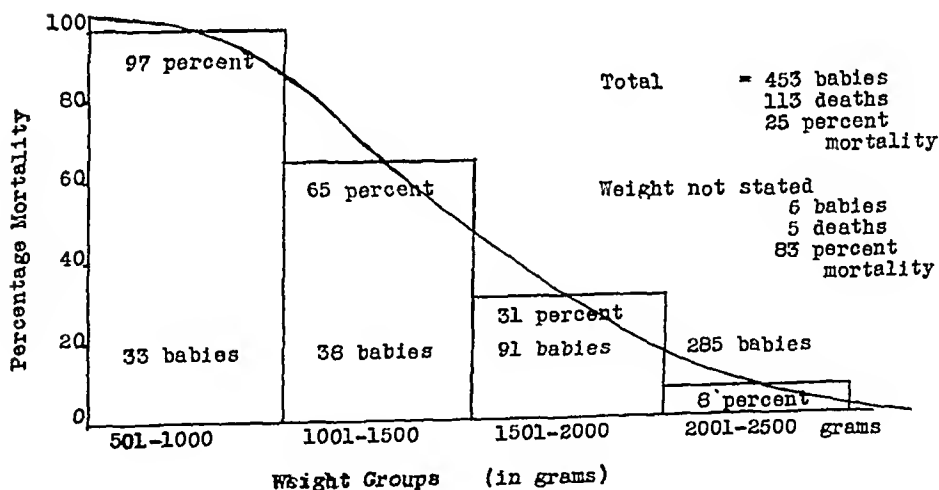


Fig. 2.

the mortality rate for that weight group; the sum of all these is then divided by the total number of cases studied. This will give the expected mortality percentage. This can then be compared with the actual mortality and difference between the two noted."

For example, let us find the expected mortality for babies born during the thirtieth and the thirty-first weeks by looking at Table IIA.

In our series there were 37 infants born at this intrauterine age. Nineteen of them died, giving a true mortality of 51.0 per cent. We find then that there was a difference between the true and expected mortality.

## PREMATURE INFANT MORTALITY\*

### A STATISTICAL STUDY OF FACTORS INFLUENCING MORTALITY IN 453 INFANTS WEIGHING LESS THAN 2,500 GRAMS

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**A**LTHOUGH the incidence of premature births at the Evanston Hospital for a ten-year period was only 5 per cent, the deaths in this small number (113) accounted for 65 per cent of the gross neonatal mortality (174). It is obvious therefore, that any marked reduction in the gross neonatal mortality rate must be brought about by a reduction in premature births or by reducing the number of deaths in this group. In this study we have attempted to analyze certain factors which we thought might have an influence on mortality.

There were 8,456 babies delivered at the Evanston Hospital in the years 1929 to 1938 inclusive. Of these, 5 per cent, or 453, weighed 2,500 Gm. or less. It is this small group which accounted for 65 per cent of the total neonatal deaths. Of the 174 neonatal deaths, 113 were in this group. All of these 453 infants were not really premature. Many of them were from multiple pregnancies and were small even though they were at or near term. We have divided the babies into the groups according to weights; under 1,000 Gm., 1,001 to 1,500, 1,501 to 2,000, and 2,001 to 2,500 Gm., and a fifth group in which are placed those infants whose weights were not recorded. Any further division would result in such small numbers in each group that there would be errors due to sampling. Our results are summarized in ten tables.

Table I and Fig. 1 clearly show the close correlation between the weight of infants at birth and mortality. Ninety-seven per cent of those weighing 1,000 Gm. or under died, while of those between 2,000 and 2,500 Gm., only 8 per cent died.

TABLE I. RELATION OF BIRTH WEIGHT TO INFANT MORTALITY  
MORTALITY FOR WEIGHT GROUPS

GROUPS	TOTAL	LIVED	DIED	PER CENT DIED
Under 1000 Gm.	33	1	32	97
1001 to 1500 Gm.	38	13	25	65
1501 to 2000 Gm.	91	63	28	31
2001 to 2500 Gm.	285	262	23	8
Weight not stated	6	1	5	83
Total	453	340	113	25

Table II and Fig. 2 show the intrauterine age of the babies at birth. It is readily seen that most of those under thirty weeks' gestation weighed 1,500 Gm. or less, and practically all of those thirty-four weeks' gestation or more weighed over 1,500 Gm. In the graph, the mortality curve for intrauterine age at birth and that for weight are nearly parallel. Since intrauterine age could not be accurately determined, we have taken weight as the most reliable single factor in determining prematurity.

\*Presented at a meeting of the Chicago Gynecological Society, October 20, 1939.



TABLE IIA. TRUE AND EXPECTED MORTALITY

WEEKS OF GESTATION	WEIGHT IN GRAMS					TOTAL NO. OF BABIES	DIED
	500-1,000	1,001-1,500	1,501-2,000	2,001-2,500	NOT STATED		
30-31	1	11	18	6	1	37	19
Weight-Mortality per cent	97	65	31	8	83		

True Mortality: $19 \times 100$	Expected Mortality: $97 \times 1 = 97$
$\frac{37}{97} = 51.0\%$	$65 \times 11 = 715$
	$31 \times 18 = 558$
	$8 \times 6 = 48$
	$83 \times 1 = 83$
	$\frac{1501}{37} = 40.5$ per cent
	$\frac{1501}{37} = 40.5$ per cent

## PARITY AND SEX

While there were more primiparas than multiparas, the true infant mortality for each group was 24.6 and 25.4 per cent, respectively, a negligible difference. Table III shows there was practically no difference between the true and expected mortality. From this it would seem that parity had no influence on fetal mortality.

It is a well-known fact that more male than female infants are born. In our series of premature infants the reverse was found; 239 females to 214 males. Nevertheless there were more deaths in males than in females, with a true mortality for males of 30 per cent and for females 21 per cent. Eliminating the weight factor, the expected mortality was the reverse; 21.9 per cent for males and 24.7 per cent for females. While this fact is interesting and has been noted by other investigators, no explanation will be attempted (see Table IV).

## RELATION OF INCIDENTS OF LABOR AND DELIVERY TO MORTALITY

To determine the effect of length of labor on mortality, an analysis was made of periods of five hours. The true and expected mortalities were essentially the same. But curiously enough the highest rate was found in those with the shortest labor or no labor at all, for example, when delivery was by elective cesarean section. In the groups in which labor was eleven to fifteen hours, or over twenty-one hours, the mortality was the lowest. This can possibly be explained best on the fact that in the former many of the cesarean sections were done because of serious maternal pathology, such as abruptio placentae. In the short labors, contractions were probably frequent, long and violent, with consequent injury to the babies.

A consideration of the effect of the method of delivery on mortality revealed that the true and expected mortalities were very nearly the same. The lowest mortality was in delivery by forceps. The same observation has been made in similar investigations. The highest mortality occurred in the group delivered by version and extraction. This, no doubt, is due to the fact that we rarely do this operation except in emergencies, such as placenta previa. The next highest rate was in the spontaneous deliveries. The mortality rate for cesarean section was slightly higher than average, but is not unduly high, when one considers that it was done frequently for serious maternal pathology.

## EFFECT OF SEDATIVES AND ANESTHESIA

It has long been the belief that sedatives and anesthesia have a harmful effect on the newborn. Over one-third of the mothers of these babies received some form of sedation as well as anesthesia in labor. Nevertheless the mortality for these babies was only 19 per cent, which was the same as the rate for infants whose mothers had "local infiltration only." This is lower than the gross average mortality, 25 per cent. In the groups in which "sedative only" and "general anesthesia only" were used the mortality was 26 and 27 per cent, respectively. The group in which "no medication or anesthesia" was given, was the highest, 44

TABLE II. PERIOD OF GESTATION

WEEKS OF GESTATION	UNDER 1,000 GM.		1,001 TO 1,500 GM.		1,501 TO 2,000 GM.		2,001 TO 2,500 GM.		NOT STATED		TOTAL			PERCENTAGE	
	L*	D	L	D	L	D	L	D	L	D	L	D	T	TRUE	EXPECTED
38-40	0	0	0	0	2	2	93	7	0	0	95	9	104	8.5	8.8
36-37	0	0	1	1	14	3	70	0	0	0	85	4	89	4.5	13.6
34-35	0	0	2	0	13	5	56	5	0	0	71	10	81	12.0	14.5
32-33	0	1	4	2	18	7	18	7	0	0	40	17	57	30.0	25.0
30-31	1	0	3	8	9	9	5	1	0	1	18	19	37	51.0	40.0
Under 30	0	28	3	14	1	1	3	0	1	4	8	47	55	85.0	78.0
Not stated	0	3	0	0	6	1	17	3	0	0	23	7	30	23.0	22.0

\*L, lived; D, died; T, total.



TABLE III. RELATION OF PARITY TO INFANT MORTALITY

	UNDER 1,000 GM.				1,001-1,500 GM.				1,501-2,000 GM.				2,001-2,500 GM.				NOT STATED				TOTAL				PERCENTAGE	
	L		D		L		D		L		D		L		D		L		D		L		D		TRUE	EXPECTED
	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D		
Primiparas	0	18	9	11	37	17	143	11	37	17	143	11	190	62	252		190	62	252		190	62	252		24.6	25.5
Multiparas	1	14	4	14	26	10	115	12	26	10	115	12	146	50	196		146	50	196		146	50	196		25.5	24.4
Not stated	0	0	0	0	0	1	4	0	0	0	0	0	4	1	5		4	1	5		4	1	5		20.0	12.6

TABLE IV. MALES AND FEMALES

	UNDER 1,000 GM.				1,001-1,500 GM.				1,501-2,000 GM.				2,001-2,500 GM.				NOT STATED				TOTAL				PERCENTAGE	
	L		D		L		D		L		D		L		D		L		D		L		D		TRUE	EXPECTED
	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D		
Males	0	16	4	14	25	17	122	13	25	17	122	13	151	63	214		151	63	214		151	63	214		30	24.9
Females	1	16	9	11	38	11	140	10	38	11	140	10	189	50	239		189	50	239		189	50	239		21	24.7

per cent. This undoubtedly is an unfair figure because the number of cases was so small in that group. Although we have used sedatives and anesthesia to this extent in all groups, it does not appear from these figures that they have a notably harmful effect (see Table VII).

#### EFFECT OF MATERNAL MORBIDITY ON INFANT MORTALITY

In the same manner, eliminating the weight factor, a study was made of the true and expected mortality in relation to various pathologic conditions present in the mother. In 282, or 63 per cent, no pathologic condition was recorded. As one would expect, the mortality rate was lowest in this group. According to our figures, toxemia in the mother had no effect on infant mortality, as a matter of fact the rate was lower than the average and lower than the expected mortality. Premature rupture of the bag of waters showed an increase in infant mortality. While this condition is not strictly speaking maternal morbidity, we have included it here. As one would expect, the rates for abruptio placentae and placenta previa were high. Hydramnion showed the highest rate, 77.7 per cent for true and 66.5 per cent for expected mortality. Nineteen other cases were grouped under the heading of "other pathology;" these were only 4.1 per cent of the entire group, and we did not wish to divide them any further. The diseases included were: pyelitis, cardiac decompensation, carcinoma of the bowel and stomach, hyperthyroidism, pulmonary tuberculosis, and trauma from a fall. These conditions were all severe enough to have had directly or indirectly considerable influence on the infant mortality rate. This was quite high, the true rate being 36.8 per cent.

#### THE AGE AT DEATH OF THE 113 INFANTS WHO DIED

Table IX shows that 72 per cent of the infants who died, lived less than twelve hours. However, it must be stated that every infant who breathed at all, or whose heart was beating at birth has been included in this number. Many of them lived but a few minutes. It is obvious that this most critical time in a premature infant's life should receive the greatest study from the standpoint of aftercare. A discussion of the effect of infant care on mortality is not within the scope of this report.

TABLE IX. THE AGE AT DEATH OF 113 INFANTS

FIRST 12 HR.		12-24 HR.		24-48 HR.		3RD-10TH DAY		OVER 10 DAYS	
NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
82	72	12	11	7	6	6	5	6	5

Ninety-four per cent of the babies in this report who died were studied at autopsy. Too often the findings were inadequate to explain the specific cause of death. This is shown in Table X where it is seen that 63.7 per cent were reported as having died of prematurity or "congenital weakness." Actually this is not an anatomic cause of death but a physiologic state. In another 4.4 per cent, atelectasis was given as a cause of death, which likewise, to a great extent, is

TABLE X. CAUSE OF INFANT MORTALITY

CAUSES OF DEATH	UNDER 24 HOURS	2 TO 7 DAYS	8 TO 14 DAYS	OVER 14 DAYS	TOTAL	PER CENT
"Congenital weakness"	65	5	2	0	72	63.7
Asphyxia	14	0	0	0	14	12.3
Cerebral hemor- rhage	8	6	0	0	14	12.3
Atelectasis	4	1	0	0	5	4.4
Malformation	2	0	2	0	4	3.6
Pneumonia	1	1	0	1	3	2.7
Acute enteritis	0	0	0	1	1	.9
Total	94	13	4	2	113	99.9
Per cent	83.2	11.5	3.5	1.8		

TABLE VII. EFFECT OF SEDATIVE AND ANESTHESIA ON INFANT MORTALITY

	UNDER 1,001- GM.				1,001- 1,500 GM.				1,501- 2,000 GM.				2,001- 2,500 GM.				NOT STATED				TOTAL				PERCENTAGE	
	1,000 GM.		1,500 GM.		2,000 GM.		2,500 GM.		3,000 GM.		3,500 GM.		4,000 GM.		4,500 GM.		5,000 GM.		5,500 GM.		6,000 GM.		TRUE	EXPECTED		
	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D				
None	0	3	0	5	2	0	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10	8	18	44	41
Local infiltration	0	1	3	0	6	3	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	17	4	21	19	30
Sedative only	0	3	0	1	2	1	12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14	5	19	26	28
Only anesthesia	1	20	9	13	34	15	128	13	0	3	0	3	0	3	0	3	0	3	0	3	0	172	64	236	27	27
Sedative and anesthesia	0	5	1	6	19	8	104	10	1	1	1	1	1	1	1	1	1	1	1	1	1	125	30	155	19	18
Not stated	0	0	0	0	0	1	2	0	0	1	0	0	0	1	0	1	0	1	0	1	2	2	4	50	42	42
Total	1	32	13	25	63	28	262	23	8	1	5	1	5	1	5	1	5	1	5	1	340	113	453	25	25	25
Per cent mortality	97				65				31				8				83				31					

TABLE VIII. EFFECT OF MATERNAL MORBIDITY ON INFANT MORTALITY

	UNDER 1,000 GM.				1,001-1,500 GM.				1,501-2,000 GM.				2,001-2,500 GM.				NOT STATED				TOTAL				PERCENTAGE	
	L		D		L		D		L		D		L		D		L		D		L		D		TRUE	EXPECTED
	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D				
No pathology	0	15	5	10	42	7	178	20	1	4	1	4	226	56	282	19.8	20.3									
Toxemia	1	2	5	3	10	8	34	1	0	0	0	0	50	14	64	21.8	25.7									
Premature rupture of bag of waters	0	4	1	7	7	7	32	0	0	0	0	0	40	18	58	31.0	27.5									
Abruption placentae	0	1	0	0	0	0	4	1	0	0	0	0	4	2	6	33.0	22.9									
Other pathology	0	2	0	3	2	2	10	0	0	0	0	0	12	7	19	36.8	36.0									
Placenta previa	0	4	1	0	2	4	3	0	0	0	1	1	6	9	15	60.0	49.2									
Hydramnion	0	4	1	2	0	0	1	1	0	0	0	0	2	7	9	77.7	66.5									
Total	1	32	13	25	63	28	262	23	1	5	1	5	340	113	453											

DR. FREDERICK H. FALLS.—It is easy for the obstetrician to transfer his responsibility to the pediatrician. There is too often a tendency for the obstetrician to wash his hands of the care of the baby after its immediate birth.

Most people who have been entrusted with the conservation of life of these premature have recognized that the preservation of body heat is a very important point. To that end, for a good many years, we have used a foot bath on the delivery room table. As soon as the baby comes out of the liquor amnii we put it in the warm water even before we cut the cord. We keep the water warm by adding hot water while we are sucking the mucus out of the pharynx and waiting for or establishing respiration. Then we remove the baby from the warm bath direct to warm blankets and then to the incubator.

We feel also that the most important thing in the management of premature babies is to prevent prematurity. The cause of prematurity is undue uterine irritability. The best way we have of preventing undue uterine irritability is to use a sedative to stop uterine contraction. The best sedative we have for this purpose is the corpus luteum extract, progesterone.

In cases of premature rupture of the membranes, placenta previa and premature detachment of the placenta in which it is only partially detached, a live baby may die if expelled, because of its prematurity. If you give a progestin preparation in sufficient amount so that it will stop uterine contractions, it will stop bleeding from the placenta previa and premature separation of the placenta. We have been able to control such bleeding for over three months, and we have been able to prevent abortion following rupture of the membranes for six weeks.

DR. DAVID S. HILLIS.—The proper management of a baby, born prematurely or in poor condition from any cause, should begin immediately after birth and this is part of the responsibility of the obstetrician. Every delivery room should have available an oxygen chamber automatically warmed and humidified which contains a concentration of oxygen of 50 per cent or more. Experience with this sort of device has given me a strong conviction that it is a valuable and necessary part of modern obstetric equipment. When the baby has gained strength after a few hours in such a chamber, it may then be transported to the premature nursery which will be so equipped that similar treatment may be continued as long as needed.

DR. LUSSKY (closing).—Reducing the premature infant mortality rate is a task which can be accomplished only by the joint efforts of the obstetrician and pediatrician. The pediatrician is primarily concerned with devising better methods and means for saving the infant after it is born. The obstetrician is primarily concerned with the problem of delaying birth as long as possible, or at least, as long as it is in the best interests of either the mother or infant.

The report shows that 83 per cent of the deaths occurred during the first twenty-four hours and that autopsy demonstrated an anatomic cause for death in only 32 per cent of the cases. In 64 per cent of the cases, the cause of death had to be ascribed to prematurity or congenital weakness. These probably were immature babies who simply cannot cope with external conditions no matter what we do or how hard we try. This group of infants would be greatly benefited if their intrauterine existence could be lengthened. But since at present this seems to be an impossibility, we must do the best we can with infant care and treatment.

No mention is made in this report on the influence of treatment in reducing the mortality. It is almost impossible to evaluate the effect of treatment, on account of the great number of unknown variables. Treatment is largely symptomatic. The physiologic condition of the infant, the pathologic condition in the infant, the effect of the length of labor, anesthesia, and pathologic conditions of the mother, etc., upon the individual infant are quantities which we are unable to determine accurately in our present state of knowledge.

The discussions have brought out several interesting points in regard to treatment. Delay in cutting the cord and stripping undoubtedly add to the infant's blood supply. Applying heat and giving oxygen are mainly symptomatic treatment, since most of these infants that die, succumb in the first twenty-four hours, before it is possible to make any accurate diagnosis. We have not as yet found means of supplying the premature infant with surroundings comparable to those in utero.

a physiologic state. In only 32 per cent could an anatomic cause of death be found; asphyxia and cerebral hemorrhage each 12.3 per cent; malformation 3.6 per cent; pneumonia 2.7 per cent; and acute enteritis 0.9 per cent. Only such cases, in which definite obstruction was found, were considered as having died of asphyxia.

### CONCLUSIONS

1. The mortality for infants weighing less than 2,500 Gm. increases as the weight decreases.
2. The mortality rate increases as the intrauterine age at birth decreases.
3. The mortality curves for weight and intrauterine age are very nearly parallel.
4. Of all the criteria for determining prematurity, weight was the most reliable single factor.
5. The infant mortality rate was essentially the same for primiparas as for multiparas.
6. The number of female infants definitely exceeded the number of males, which is contrary to the ratio found for all infants at birth.
7. The death rate for male infants was practically 50 per cent greater than for females.
8. The length of labor apparently had very little effect on infant mortality.
9. The type of delivery seemed to have no pronounced effect on mortality.
10. The use of sedatives and anesthesia did not show an adverse effect on mortality.
11. Morbidity was found in 37 per cent of the mothers and had a definite effect on the infant mortality; most pronounced in accidents of labor and hydramnion, and least in toxemia.
12. The first twelve hours was the most critical time in these infants' lives and from the standpoint of infant care is the period that should receive thorough study.
13. In only 32 per cent of the infants who died could an anatomic diagnosis be established. Congenital weakness and atelectasis are not anatomic causes of death.

### DISCUSSION

DR. EDWARD L. CORNELL.—I had been very enthusiastic about the care of small premature babies until a certain case which occurred in my private practice. I had thought I was very smart in keeping alive small premature twins only to find that they were idiots. They are still alive after two years. I think we should make every effort to keep alive babies that weigh 2,000 Gm., but where they are under 1,500 Gm., I have my doubts as to whether a large percentage will turn out to be perfect babies.

DR. HENRY J. ZETTELMAN.—By cutting the cord early or late, one may somewhat influence the blood picture in the newborn. In the past we have been taught to allow the baby to remain attached to the mother until the cord stops pulsating. That is not always feasible because the cord will pulsate for forty-five minutes. In several cases it has been possible to show that by cutting the cord immediately after the baby is born, the hemoglobin will be only 13 to 15 Gm., but if you allow the cord to remain uncut you can produce a hemoglobin of 22 to 25 Gm., and the red count will go up to 6,500,000. Is it not possible that in an effort to get these premature babies into a warm incubator, we cut the cord too early and prevent valuable blood coming to the baby?



Corpuscles may contain one or both of two substances called A or B. Serum may similarly contain one or both of two agglutinating substances, a and b, acting on cells containing A and B, respectively. A and B therefore, can never be found in the blood of a child unless they are present in that of the father or mother. In our series, 45 per cent of fetal bloods were of different type than the mother's blood.

Fetal blood has the advantage of being free of allergens so that food and other extraneous allergic reactions are eliminated. A Wassermann reaction is not done on the cord blood because the mothers are tested routinely in the clinic, and the maternal Wassermann is said to be more reliable than the cord Wassermann.

#### PRESERVATIVE AND FLASKS

The preservative used in this series is that proposed by the Moscow Institute of Hematology and recommended by Goodall and his co-workers in their report. It consists of: Sodium chloride, 7.0; sodium citrate, 5.0; potassium chloride, 0.2; magnesium sulfate, 0.004; and bi-distilled water, q.s. 1000.

This solution is prepared in ampoules ready for use, but the price was prohibitive so, for a small sum, the above chemically pure drugs were bought in quantities and the hospital pharmacist dissolves the above formula in three ounces of distilled water, and these three-ounce bottles are kept on hand for use in filling the flasks. We use a 250 c.c., widemouth, Erlenmeyer flask which we have graduated at 100, 150, and 200 c.c. by scratching with a diamond pencil. A cotton plug covered with gauze is fitted in the mouth of the flask, and this is covered with a large flat piece of cotton covered with gauze, the ends of which are tied around the neck of the flask. As the plugs and covers usually are soiled with blood new ones are made each time the flasks are used again. A three-ounce bottle of preservative is emptied into a liter graduate and diluted to 1000 c.c. with triple distilled water. This is filtered through fine paper and 100 c.c. placed in each flask which has been thoroughly cleaned and rinsed with distilled water. The stoppers and top coverings are fastened in place and the flasks are autoclaved at 260° and 20 pounds pressure for twenty minutes. They are then stored in a convenient shelf in the delivery room. About 2 c.c. of the preservative are placed in each of an equal number of small test tubes which have rubber stoppers and are not autoclaved. These tubes are stored with the flasks and at the time of collection are attached to the flask and used for typing and cross agglutination.

Approximately equal parts of blood and preservative are used, and as our average yield is 75 c.c., we place 100 c.c. of the preservative in the flask as this will take care of the average collection. The flasks being calibrated at 200 c.c. we take no more than that amount in cases of heavy yield.

Two English writers<sup>2</sup> criticize this preservative saying that there is clotting and hemolysis due to insufficient citrate and hypotonicity. They recommend 0.3 Gm. of sodium citrate in 10 c.c. of distilled water. Another group<sup>4</sup> recommend 1 Gm. of sodium citrate in 80 c.c. of twice-distilled water but say that citrate-saline solutions are best. A Boston group<sup>5</sup> uses 15 c.c. of 2.5 per cent sodium citrate. In Palestine<sup>3</sup> a 3.8 per cent sodium citrate solution is used. In comparing the preservative we use with sodium citrate in saline, we found that 0.4 per cent, 0.5 per cent, and 0.6 per cent sodium citrate in saline preserved the blood in a similar state to that of our preservative. The gross hemolysis, shape of the red blood cells, hemoglobin, red count, white count, and differential behave similarly during the storage. In 0.1 per cent sodium citrate there was marked hemolysis, destruction of the red cells and clotting; 0.2 per cent and 0.3 per cent were slightly better but still presented clotting and hemolysis. In a personal communication from Dr. DeGowin of the University Hospitals of the State University of Iowa, he states that a mixture of dextrose and citrate will keep blood satisfactorily for one month, at the end of which time the hemolysis is about  $\frac{1}{25}$  to  $\frac{1}{50}$  as much as in citrated blood or in citrate plus saline. His work has been done almost wholly with adult blood, but he thinks it applicable to placental blood. This mixture of dextrose and citrate will probably be investigated with placental blood at the Kensington Hospital.

## EXPERIENCES WITH A PLACENTAL BLOOD BANK\*

W. MEREDITH HEYL, M.D., PHILADELPHIA, PA.

(*From the Kensington Hospital for Women*)

THE development of the use of stored blood which has become both practical and popular in the past few years has stimulated a search for new sources of this valuable material and better means of preserving it. The most common source of stored blood is from volunteer donors from whom the blood is taken as in indirect transfusion and stored for future use. The Blood Bank at the Philadelphia General Hospital is illustrative of this method. Then there is that group of patients including cardiac decompensations, polycythemia, etc., where venesection is indicated. Now, instead of being discarded, this blood is collected under sterile precautions, citrated, and stored for use in transfusion. Russian authors have proposed and report success with the collection and preservation of cadaver blood, taken from cases of accidental death or similar conditions where no pathology is present. They also were apparently the first to suggest the use of placental blood for transfusion. Since then there have come favorable reports of its use from England, Canada, Palestine, and the United States, the only question being the preservative to be used. The Placental Blood Bank at the Kensington Hospital for Women was set up in January, 1938, and has been in operation since then.

### PLACENTAL BLOOD

Placental, or fetal, blood differs from adult blood in several ways. The hemoglobin and morphologic elements are increased. Hemoglobin,<sup>1</sup> 120 per cent (16 Gm. equals 100 per cent), red cells 5,500,000, white cells 20,000, of which 60 per cent are polymorphonuclears, 30 per cent lymphocytes, and 10 per cent monocytes. The quantity obtainable for collection varies widely from 30 to 200 c.c., but our average was about 75 c.c. Other writers report averages of 47 c.c.,<sup>2</sup> 55 c.c.,<sup>3</sup> 80 c.c.,<sup>4</sup> 105 c.c.,<sup>5</sup> and 125 c.c.<sup>6</sup> The blood is said to have<sup>7</sup> considerable bilirubin content, high sugar content, low cholesterol and alkali reserve, increased potassium and calcium, lower albumin content. It is said to contain estrogen, gonadotropic substance and an epinephrine-like substance. It is distinguished by its rapid coagulability. The blood may contain anesthetic or analgesic drugs used during labor, and recipients have been reported<sup>5</sup> to have complained of an ether taste after receiving a placental blood transfusion. We have had no such incidents. A report from Palestine<sup>3</sup> says that the blood is safe against malaria, as the organism does not pass the placenta, and in preserved blood the plasmodium quickly dies. The blood has a definite blood group or type and the fetal blood does not as one Russian writer<sup>7</sup> states, "always correspond to that of the mother's blood."

The inheritance of blood groups follows a Mendelian ratio of dominant A and B and recessive a and b.<sup>8</sup>

Type I—A and B

Type II—A and b

Type III—a and B

Type IV—a and b

\*Read at a meeting of the Obstetrical Society of Philadelphia, October 5, 1939.

When the bank was started and the studies were made on the blood, before it was used for transfusion, all of the flasks were cultured but no growth was found. Now about every tenth flask is cultured then discarded, and to date no growth has been obtained. Some writers,<sup>2</sup> using a more complicated technique of collection, have reported positive cultures in 22 per cent of the flasks, but this is the only paper reporting contamination, all others reporting negative cultures, as in our series.

### USE IN TRANSFUSION

Sufficient flasks of all types are kept in readiness for immediate use. Prenatal patients are typed in the Clinic and in case a transfusion is necessary reference to their chart will give information as to their type, so that flasks of similar type blood may be immediately crossagglutinated with the recipient. We keep more Type IV flasks than any other type for, it being the universal donor, we use it in all types of recipients and prefer it to the same type in Type II recipients. The satisfactorily crossagglutinated flasks are then warmed to body temperature in a water bath, although this is not necessary, and given with normal saline. The blood is poured through several layers of sterile gauze into the burette, for occasionally there are soft clots in the bottom of the flask. The gauze removes them satisfactorily, and we have seen no disturbance from their presence in the blood. Several flasks of the same or different type may be used in the same transfusion if each is crossagglutinated with the recipient.

### RESULTS

Between January, 1938 and July, 1939, there were 32 transfusions given to 27 patients. The number of flasks used varied from one to four with an average of 2.4 flasks with each transfusion. The average amount of blood given in each transfusion was 275 c.c., the smallest was 75 c.c. and the largest 500 c.c. In 28 of the 32 transfusions, the donor and recipient were the same type. In 3 cases Type IV blood was given to Type II recipients. In one case mixed blood was given: 3 flasks of Type IV and one flask of Type I to a Type I recipient. The age of the blood when used varied from five days to six weeks, with an average age of 2.6 weeks. The effect of the transfusion seemed equally good regardless of the age of the blood. The indications can be grouped as follows:

1. Acute hemorrhage, as post-partum hemorrhage, hemorrhage due to placenta previa or abortion, 9 cases or 28 per cent.
2. Infection, including puerperal sepsis, pyelitis, peritonitis, infected abortions, 10 cases or 32 per cent.
3. Postoperative shock after difficult operations, or more than usual blood loss and who present a rapid, weak pulse on return to bed, 5 cases or 15 per cent.
4. Secondary anemias due to bleeding fibroids, abortions or malignancy, 8 cases or 24 per cent.

There were three questionable reactions, giving a gross incidence of 9.3 per cent.

1. One patient was anemic and in shock. She had had a hysterectomy, and after a transfusion she had a slight convulsive seizure of tonic and clonic type, lasting about ten minutes. Another patient the same day had a less marked but similar seizure following intravenous infusion of saline, so they may have been due to the flasks, tubing, or saline.

2. Another patient had a chill and temperature of 105° F. following transfusion. She had an infection after an incomplete abortion, with a temperature elevation before transfusion.

3. The third was a case of sepsis. The patient had chills and fever before transfusion and a chill and temperature of 103.6° F. after transfusion.

### DISCUSSION

In presenting this technique for the preservation of placental blood and its use in transfusion, it is not suggested that this medium is superior to adult blood. In cases of elective transfusion, it is believed that adult blood is probably better and in such cases we use adult blood,

### TECHNIQUE OF COLLECTION

At the completion of the second stage of labor, the child is placed on the mother's abdomen. The cord is immediately tied with tape and about 15 cm. of the cord distal to the tie is cleansed with a piece of gauze saturated with 65 per cent alcohol. The cord is grasped in this sterilized area with the gauze, pressure is exerted, and the cord cut with sterile scissors. A nurse, not scrubbed, removes the top covering of the flask, keeping the cover free of contamination, and holds the flask for collection. The operator removes the sterile plug and holds the end of the cord over the flask but not touching it and releases pressure on the cord allowing the blood to flow into the flask. By allowing slack in the cord and having the gauze well wrapped around it, there is prevented any contamination by amniotic fluid or other materials running down the cord. As the flow decreases the cord may be milked with care and more blood obtained. When the flow stops the sterile plug is reinserted in the flask by the operator and the uncontaminated tap gauze cover replaced by the nurse, who then holds an unsterile test tube for collection of a few drops of blood in the same manner. The cord is then clamped and attention paid to the third stage of labor. The small tube is attached to the flask with adhesive on which is written the mother's name, the date and later the type of placental blood.

There are certain contraindications to the collection of placental blood for storage. Any condition of the child or mother requiring the immediate attention of the operator would, of course, cause the procedure to be abandoned. Known transmissible diseases of either mother or child, as syphilis or tuberculosis, contraindicate collection of placental blood. Blood is not collected in cases in which the membranes have been ruptured forty-eight hours before delivery or where there is unusual soiling of the vagina as in extensive operative delivery. Eclampsia or toxemia is not, in itself, a contraindication. Premature infants have cords with so little blood that its collection is not warranted.

### STORAGE

After collection the flasks are placed in a refrigerator with a temperature of 34° to 38° F. Temporary changes in temperature do not affect the character of the blood so that the refrigerator may be defrosted without moving the blood. It is said that the blood settles into three layers. The top is a supernatant fluid which is clear at first but becomes colored as hemolysis progresses; the middle layer is a thick buffy coat and the bottom layer is composed of red blood cells. There are progressive and definite changes which occur in the cellular elements of the blood during storage. There is a progressive hemolysis which is evident in the coloring of the supernatant fluid and in the changes in blood counts. This hemolysis is hastened by shaking or unnecessary movement of the blood. Even in considerable degree the hemolysis does not interfere with a satisfactory transfusion. In our series the following studies were done at the time of collection and at weekly intervals for four weeks: Hemoglobin determination by the Sahli technique, red and white cell counts with differential and fragility tests. The hemoglobin remained about the same, being 42 per cent at time of collection and 38 per cent four weeks later. The red cells dropped progressively, being 1,620,000 at time of collection; 1,500,000 the first week, 1,170,000 the second week, 800,000 the third week, and 590,000 the fourth week. The white cells showed the greatest change, there being a complete disappearance of the granular series in the four weeks.

	WHITE BLOOD COUNT	POLYMORPHO- NUCLEARS	LYMPHO- CYTES
At time of collection	2,940	68%	32%
First week	1,020	22	78
Second week	680	6	94
Third week	630	3	97
Fourth week	450	0	100

There was progressive increase in the fragility of the red cells. At time of collection the range was 0.42 to 0.28, in the first week 0.48 to 0.32, and by the second week it had reached 0.50.

## INTERMENSTRUAL PAIN—A SURGICAL CONDITION\*

EDWARD FRANCIS McLAUGHLIN, M.D., PHILADELPHIA, PA.

**I**N SOME women there occurs discomfort, sometimes true pain, midway between menstrual periods or in the latter half of the menstrual cycle. This is considered a normal occurrence by some observers, especially in its milder forms. However, I regard it as abnormal and believe it is due to the rupture of small simple ovarian cysts or hemorrhage into them. When this pain grows severe enough for the sufferer to consult a doctor, it becomes a surgical problem, because it calls for differentiation from other conditions giving similar signs and symptoms which require immediate or elective operation.

Cases of intermenstrual pain are encountered most often by the general surgeons and are studied and reported almost exclusively by gynecologists. Wharton and Henriksen<sup>1</sup> among others speak of its frequency, yet the number of cases recorded in the literature is comparatively small.

First to describe intermenstrual pain in English was Sir W. O. Priestley before the Royal College of Physicians in London. He<sup>2</sup> published his observations in the *British Medical Journal* in 1872 and accurately described the clinical aspects of the midcycle type of pain and speculated with remarkable exactness that its cause lay in some disturbance of the process of ovulation which he placed ten to fourteen days before an oncoming period. He mentions work done by Bischoff in Germany and Poucet and Coste in France. Fehling<sup>3</sup> in 1881 advanced the theory of uterine contractions as a cause. H. Wilson<sup>4</sup> in 1905 first described hemorrhage from a ruptured Graafian follicle, noted at operation. Novak<sup>5</sup> in 1914 and in 1917<sup>6</sup> also added to the literature on the subject, especially on ovarian hemorrhage and stated "hematomas of the ovary are very common and are almost always caused by hemorrhage into the lumen of an atretic follicle or corpus luteum," a fact which seems to have been lost sight of or disregarded. In 1924 Phaneuf<sup>7</sup> brought out the difference between follicle and corpus luteum cysts. Pratt<sup>8</sup> in 1934 ascribed the "mittelschmerz" to irritating fluid from ruptured follicles, follicle cysts, or corpus luteum cysts. Hoyt and Meigs<sup>9</sup> in 1936 were the first to describe ruptured follicle and corpus luteum cysts as a surgical entity to be differentiated from acute appendicitis or ruptured ectopic pregnancy. They reported 58 cases and concluded that "discomfort in any woman in the supposed time of ovulation to the oncoming menses may be due to rupture or bleeding."

Also in this same year an article in the *J. A. M. A.* by Wharton and Henriksen<sup>1</sup> dealt with "Operative Observations in Periodic Intermenstrual Pain." Nine patients were operated upon at the time of pain; all had ruptured follicles. They proved this to occur simultaneously with ovulation in their cases. A distinction was made between acute and mild cases.

In 1937, Israel<sup>10</sup> pointed out that "the ruptured portion of the ovary is usually adherent to the posterior surface of the uterus and exhibits a hemorrhagic excrescence of varying size"—the first mention of the formation of adhesions.

De los Santos<sup>11</sup> reports a fatality from an overwhelming hemorrhage arising from a ruptured follicle cyst.

During this present year (1939) three excellent studies have been published on this subject, one by Pierra,<sup>12</sup> the second by Harris and Groper,<sup>13</sup> and the third by Weil.<sup>14</sup>

\*Read at a meeting of the Obstetrical Society of Philadelphia, October 5, 1939.

as 61 indirect transfusions of adult blood, as compared with 32 transfusions of placental blood, were given in the same period of time. However, in cases of emergency where blood is needed immediately, or, when in elective transfusion there is difficulty in finding a suitable donor, we feel that placental blood fulfills the requirements satisfactorily; especially when we have such an abundance of the medium which is so easily collected and preserved.

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438 EAST DURHAM STREET

# DISCUSSION

DR. EDWARD SCHUMANN.—In this technique, the promised transfusion can be done in twenty minutes and then, at leisure, the donors obtained for the much more valuable transfusion of adult blood. We have found it is a method which gives us great confidence and no member of the Staff would consent to abandoning the placental blood bank.

DR. CARL HENRY DAVIS.—It might be interesting in discussion to describe briefly the original blood bank in Moscow. In 1935 I spent a day with Judin, who developed the use of cadaver blood for transfusion. He citrated the blood in the first 300 collections of blood from dead people, but later discovered that this was not necessary. Since learning this, they have drawn the blood directly into sterile flasks and the flasks are placed in an ice box for two or three days before examination. After drawing the blood from the body, there is a very thorough autopsy. If there is evidence of disease, the blood is destroyed; if the body is healthy and the blood does not coagulate after being placed in the ice box, it is checked for syphilis, and a culture is made. At the end of a week, if all examinations indicate it is free from contamination, it is grouped. No blood is used in less than eight days from the time it is drawn from the cadaver.

We witnessed the process of drawing the blood. In a city like Moscow, they have a great many sudden deaths where the individual has not been greatly traumatized. Of course, a crushing injury rules out the possibility of the blood being used. If one dies of a sudden heart attack, etc., without definite disease, the blood should be suitable for transfusion. At any time within the first two hours after the death, the body is placed upon a table similar to that used for tonsillectomies, so that it is possible practically to stand the corpse on his head. With surgical precautions such as in an operating room, cannulas are placed in the veins on either side of the neck and the blood is drained through sterile tubes into flasks. With the feet up in the air the blood very rapidly fills the flasks. In that hospital, Dr. Judin said, the blood bank meant the saving of many lives.

Conserving blood from the placental circulation as described, seems like an excellent way to secure blood for a blood bank, and the reports thus far are favorable. Unfortunately, in the one patient where I used infants' blood, there was a rather severe reaction, but this probably resulted from some slip in technique.

TABLE I. LOCATION AND TYPE OF ONSET OF PAIN

	GROUPS*			
	I	II	III	IV
Lower right quadrant	29	12	11	6
Lower left quadrant	11	3	6	2
Lower abdomen	6	4	1	1
Lower midabdomen	3	1	1	1
Unrecorded	8	2	4	2
Rapid onset	18	5	8	5
Slow onset	39	17	15	7

\*In the tables, the whole group is designated Group I, cases of intracystic hemorrhage are designated Group II, those of cyst rupture into the peritoneal cavity, Group III, and the nonoperative cases, Group IV.

TABLE II. ABDOMINAL TENDERNESS

	GROUPS			
	I	II	III	IV
Right	40	14	16	10
Left	4	2	1	1
Both	7	2	5	0
None	4	2	1	1
Unknown	2	2	0	0

TABLE III. PREOPERATIVE FINDINGS

AVERAGE	GROUPS			
	I	II	III	IV
Temperature	98.73	98.9	98.6	99.4
Pulse	90.98	89.5	92.2	91.1
White blood count (in 50 cases)	10,435	9,295	10,766	13,016
Polymorphonuclears (in 39 cases)	72%	74.67%	74%	70.6%

TABLE IV. OPERATIVE FINDINGS AND PROCEDURES

	GROUPS		
	I	II	III
<i>Operative Findings:</i>			
Right ovary involved	29	12	17
Left ovary involved	16	10	6
Adhesions	7	3	4
<i>Operative Procedure:</i>			
Removal of cyst and closing defect	24	8	16
Salpingo-oophorectomy	15	10	5
Oophorectomy	6	4	2

It is of interest to compare these signs and symptoms of Groups II and III with the operative findings in the same groups, as exhibited in Table IV. Here the involvement, while definitely more on the right, especially in the ruptured cyst cases, is not so in as great a proportion as one would expect from the preponderance of right-sided symptoms and signs.

Unlisted in tabular form but of some importance is the fact that 28 of the patients were married and 29 were single. Besides appendicitis, ectopic pregnancy was the primary diagnosis in one case, pelvic inflammatory disease in two, functional bleeding in one, and gastroenteritis or rheumatic fever in one other. Of the patients coming to operation, a correct diagnosis was made preoperatively in 31.2

## PATHOLOGY

The occurrence of follicle and corpus luteum cysts, the simple cysts of the ovary, is well known, and their structures has frequently been described. Why they occur is not clearly understood, though several explanations have been advanced.

Such cysts may rupture and discharge their contents into the free peritoneal cavity with or without hemorrhage; or bleeding may occur within the cyst itself.

Underlying the symptom of intermenstrual pain is either first, the acute hyperemic reaction of the peritoneum to the escaped fluid (Israel<sup>10</sup>) or second, the distention of the cyst itself with blood. Of this latter condition, Hertzler<sup>15</sup> says, "Every possible degree of hemorrhage is observed. Small follicles partly or completely filled with blood are common. Not infrequently, cysts of the size of a walnut occupying the entire ovary, are filled with recently clotted blood."

## PRESENT STUDY

Fifty-seven case histories have been analyzed. Five of the patients were nonhospitalized; one was in the Chestnut Hill Hospital, 12 in the Hospital of the University of Pennsylvania, and 39 in the Germantown Hospital. Both private and ward cases are included. They were cared for by different physicians. We, therefore, believe this study represents a fair cross section of the subject.

The statistical summary of our findings brings out several interesting points. Of the 57 patients, 22 showed intracystic hemorrhage, 23 ruptured cysts, and there were 12 who did not come to operation. The average age was 25.8 years. Of the patients 96.5 per cent were white, a striking predominance. The onset of pain was at the time of ovulation, or shortly thereafter, occurring as an average 16.6 days after the beginning of the last period. The symptoms in the intracystic hemorrhage group occurred 19.7 days after and in the "rupture" group 16.1 days after. From this, one would expect the hemorrhagic cysts to be of corpus luteum origin, and this was true. Of 22 such cases, 16 were of corpus luteum origin, 4 were of undetermined origin, 1 was of follicle and corpus luteum origin, and but 1 was from a follicle. Where ruptured cysts were found (23 times), examination revealed 11 were from corpus luteum cysts and 10 from follicle cysts, 1 of unknown type, and 1 from a mixed follicle and corpus luteum cyst.

Previous symptoms had occurred in 28 cases. Regularity of these preceding attacks was noted infrequently. A history of menstrual irregularity was obtained in only 6 instances.

Table I clearly demonstrates the more frequent occurrence of right-sided pain, and if one compares it with Table II, which shows an even greater frequency of right-sided tenderness, he may feel a little more kindly toward the surgeon who mistakes this condition for appendicitis. This mistake occurred in about one-third of all the cases. Of the 45 patients who came to operation, the primary diagnosis was appendicitis in nearly half (44.4 per cent).

Nausea occurred in 42 per cent of the cases and vomiting in only 15.8 per cent. Both nausea and vomiting occurred more frequently in the "rupture" group (52 and 26 per cent) than in the "intracystic hemorrhage" group (36 and 9 per cent). Diaphragmatic irritation was noted six times, one patient having a diagnosis of gall bladder disease with medical drainage of that viscus. A bloody or brownish discharge followed the intermenstrual pain in eight instances.

The average figures for temperature, pulse, white blood cell count, and differential count are strikingly normal. Their exact distribution among the groups is expressed in Table III.



blood to trickle in. This mixing with the peritoneal fluid will effectively mask a serosanguineous fluid already present from a ruptured cyst, and take away the only stimulus to investigate the pelvis. Intracystic hemorrhage was taken for chronic or recurrent appendicitis in seven instances. This condition is infrequently accompanied by free fluid, so in order to find it the ovaries should be examined on every possible occasion. We believe the unrecognized presence of rupturing follicles or intracystic hemorrhages to be responsible for the continuation of symptoms in many cases of "chronic appendicitis."

#### COMMENT

The appearance of the pelvis of some of these patients at operation gives rise to a plausible speculation. There are often definite adhesions present between the site of the ovarian rupture and the posterior surface of the uterus or broad ligament. Some of these adhesions certainly do not absorb completely. May they not of themselves or by the congestion they may cause, give rise to that large group of so-called "chronic pelvic inflammatory disease" cases (never proved to be of gonorrheal origin) which are seen daily in every gynecologic dispensary? It is our belief that this is the case in many instances.

The principal lesson to be learned from this study is that rupturing follicles or corpora lutea and intracystic hemorrhage do occur and may simulate acute or chronic surgical conditions of the abdomen. This should be borne in mind in patients presenting intermenstrual pain. A correct diagnosis is often possible and if arrived at, non-operative treatment is indicated. But then the possibility of future attacks must be kept in mind, because (again quoting Wharton and Henriksen<sup>1</sup>) "in these cases one is dealing not only with an isolated ruptured corpus luteum but with a recurring dysfunction of the ovary. The basic cause lies deeper and is as much a mystery today as it was to Poucet and Priestley."

#### SUMMARY AND CONCLUSIONS

1. Fifty-seven cases of ovarian dysfunction, giving rise to intermenstrual pain, are reported.
2. Twenty-three of these cases showed ruptured cysts, 10 follicle cysts, 11 corpus luteum cysts, 1 both types, 1 unreported.
3. Twenty-two cases showed intracystic hemorrhage, 16 hemorrhages into corpus luteum cysts, 4 into cysts of unreported type, 1 into a follicle cyst, and 1 into a follicle and corpus luteum cyst.
4. The present series is composed chiefly of white women of an average age of 25.8 years.
5. The right ovary is the one more often involved (64.5 per cent), though a larger group of patients have right-sided symptoms (70 per cent).
6. Accurate diagnosis was made twenty-four times or in 42.1 per cent of all patients and in 31 per cent of patients operated upon.
7. The most confusing condition was appendicitis. It was the primary diagnosis in 36.8 per cent of the patients and was mentioned in 59.6 per cent. Of the operated cases, 44.4 per cent were diagnosed primarily as appendicitis.

per cent, not attempted in 15.5 per cent, and incorrect in 53.3 per cent, a mediocre showing. Free fluid was found in but 16 of the 45 patients operated upon, being clear in 10 cases, bloody in 4, and chocolate colored in 2.

#### DIFFERENTIAL DIAGNOSIS

Cases with marked intraperitoneal hemorrhage simulating ruptured ectopic pregnancy need not be differentiated; the treatment will be the same. More of a problem is the differentiation between an unruptured or slowly rupturing ectopic and an intraeystic hemorrhage. The Friedman test should be positive if rupture has not occurred, or has but recently occurred in the pregnancy. It will be negative with eysts.

Blood sedimentation will be more rapid and more pronounced in the rupturing tubal pregnancy than where the intraeystic hemorrhage has occurred.

From pelvic inflammatory disease, temperature, pulse rate, sedimentation test, and smears would help make the distinction.

Ovarian cysts with twisted pedicles are usually large enough to be palpated, larger than the follicle or corpus luteum eysts.

From acute appendicitis some cases cannot be distinguished. However, if one has in mind the possibility of ruptured cyst or intracystic hemorrhage, he may not only save a patient from operation but himself from embarrassment. The temperature, pulse, and white count are much nearer normal in the ovarian condition. The cystic lesion is accompanied by less vomiting. There may be a history of former attacks occurring near the midcycle and perhaps accompanied by a brownish discharge. A point noticed by the author as well as others is that the pain frequently starts and stays in the lower right quadrant, whereas in appendicitis it is usually first general and later settles to its source. At times one may be able to palpate a swollen ovary through the vagina or rectum. When one encounters a pelvic appendicitis, however, it is almost impossible to make a differentiation. Temperature and pulse rate will be probably more elevated in the appendicitis, but they are weak supports on which to lean where the question is so fine.

It is with so-called "chronic appendicitis" that a better differential diagnosis could be made. One has a chance here to observe a patient more leisurely, and it will be surprising how many of the confirmatory symptoms of ovarian trouble will unfold themselves if they are but sought for. Regularity of attacks (perhaps not each successive month), occasional brownish or bloody discharge with one attack, a shifting to the left side now and then, and perhaps noting the presence of what Curtis terms "Phantom tumors"—eysts which can no longer be felt after spontaneous rupture. All these things and more will help bring about correct diagnosis.

The most inexcusable error is the failure to recognize ovarian disease when the abdomen has been opened. McBurney incisions and small right rectus openings up near the umbilicus make examination of the pelvis almost impossible. Another careless thing is the opening of the peritoneal cavity without first securing hemostasis and thus allowing

## TRANSPERITONEAL APPROACH IN THE MANAGEMENT OF INACCESSIBLE VESICOVAGINAL FISTULAS\*

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THE management of vesicovaginal fistulas located at the vault of the vagina, particularly in women who have never borne children, may be a very difficult problem. In the past two years, in my own experience, there have been two cases in women over 50 years of age, both of whom were nulliparas in whom fistulas were found at the highest part of the vagina. Both of these followed complete hysterectomy. One of these was closed by the use of an electrocoagulating wire passed through the fistulous tract in order to destroy its lining. This was done by the urologist to whom she was referred. In the second case this procedure failed to close the opening and a further attack was necessary.

In 1910, and again in 1917, Ward described a method for the closure of inaccessible vesicovaginal fistulas in which he made use of a Schuchardt incision in order to obtain approach to the area in which the fistula lay. This was a useful contribution and in many cases would be of distinct service. Transvesical operation has been suggested and successful cases have been reported. Our experience is limited to one case in which we had a failure. Extraperitoneal approach has been used by some operators.

In the case I wish to discuss a transvesical attempt to close the opening had already been made elsewhere. This had apparently only controlled the leakage for a few days, urine escaping vaginally before the patient left the hospital. Considerable thought was given to the method of attack. The method of Ward was seriously thought of and only discarded because the vagina was so narrow that a small speculum was needed to expose the opening in the vaginal vault, the ordinary size used in the adult patient being too large. The vagina would barely admit two fingers. It appeared that, in order to expose the area of the fistula and to obtain space for adequate dissection and mobilization of the vaginal and vesical tissues, an extremely deep incision would be needed. It was therefore determined to enter the abdomen and to approach the fistula from above. The history follows:

A nulliparous woman, aged 54 years, was operated upon in China, for complete hysterectomy five months before admission. The indication for this is not clear. Vesicovaginal fistula followed this operation. Two months after the hysterectomy a transvesical attempt was made to close the fistula, but this was unsuccessful. When first seen she was passing practically all of her urine through the fistula, voluminous pads being required constantly. Examination showed a recent abdominal scar, well healed. Vagina was narrow and small, admitting only a small-sized speculum at the highest portion of the vault. A little to the right of the median line a vaginal opening to the bladder was seen, through which urine was escaping.

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8. The usual operative procedure is removal of the cyst and over-sewing of the raw area.

9. No fatalities are noted.

10. The known occurrence of intracystic hemorrhage is here studied clinically and differentiated from chronic appendicitis.

11. It is suggested that adhesions from cyst rupture may give rise to a nonspecific pelvic inflammatory disease.

12. The so-called "mittelschmerz" occurred with very little regularity in this series.

13. If one is alert to the possibility of the ruptured cysts or intracystic hemorrhage, diagnosis can be made oftener and nonoperative treatment pursued.

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#### DISCUSSION

DR. EDWARD SCHUMANN.—Mittelschmerz is a regularly recurring symptom. If the patient complains of such a symptom over a long period of time, this diagnosis may be considered and inflammatory lesions ruled out. Under such conditions I see no reason for operation.

If these 57 cases were unruptured Graafian follicles or instances of intrafollicular rupture, why should one do anything to the ovary. It certainly seems very radical to remove an ovary under such circumstances. If the hemorrhage is massive, it becomes necessary to operate for the hemorrhage and ligate the bleeding vessels. Ordinarily, however, if in error one opens the abdomen for intermenstrual pain one should immediately close it again.

DR. S. LEON ISRAEL.—I believe that the diagnosis of ovarian rupture with intraabdominal hemorrhage can be made preoperatively if the physician viewing an acute or subacute abdomen bears the subject in mind. At the Massachusetts General Hospital, in 58 cases, one-third were diagnosed correctly by exerting a conscious effort to think of the condition.

It is interesting to note there is occasionally even a postoperative error. The general surgeon approaches the abdomen with a diagnosis of subacute or subsiding appendicitis, employs a McBurney's incision and, finding a slightly bulging appendix, removes it. As he works, a trickle of blood may come up from the lower abdominal cavity, the pelvis is explored, and sometimes an ovarian rent is seen. The abdomen is closed, and the pathologic report is "subacute appendicitis." Such appendices often show serosal and subserosal inflammatory reaction, particularly if some free blood has been in the neighborhood for twenty-four hours.

It is interesting to speculate on the cause of bleeding from a ruptured corpus luteum and why it does not occur more frequently. The fact is that not all bleeding is attended by symptoms in our experience. I think it is impossible, at the present time, to state why certain corpora lutea rupture without bleeding, and why certain others rupture and bleed severely.

DR. MC LAUGHLIN (closing).—In reply to the questions of Dr. Schumann, I wish to say that I was reporting what was actually done in the way of operation and was not advocating these radical measures. In defense of opening the abdomen frequently I may say that these ovaries are frequently found to be still bleeding and something must be done, even though the hemorrhage is small.

of vesicovaginal fistulas and reported 24 cases. The technique described by him was essentially that which was used by me although I had not seen his report at the time of the operation. He emphasized the importance of separating the suture lines in the bladder and in the vagina, because of the likelihood of a recurrence of the leakage if they are in contact. No method was used of securing their separation other than an attempt to so place the sutures that they would not be in contact. In 1937, Walters reported two cases in which transperitoneal repair was done. The technique in his patients did not vary materially from that described by Legueu, except that he suggested the use of a liberal amount of omental tissue which should be interposed between the two suture lines, in order to separate them effectively. He did not detach a piece of omental fat but drew the lower end of the omentum down and fastened it between the bladder and the vagina.

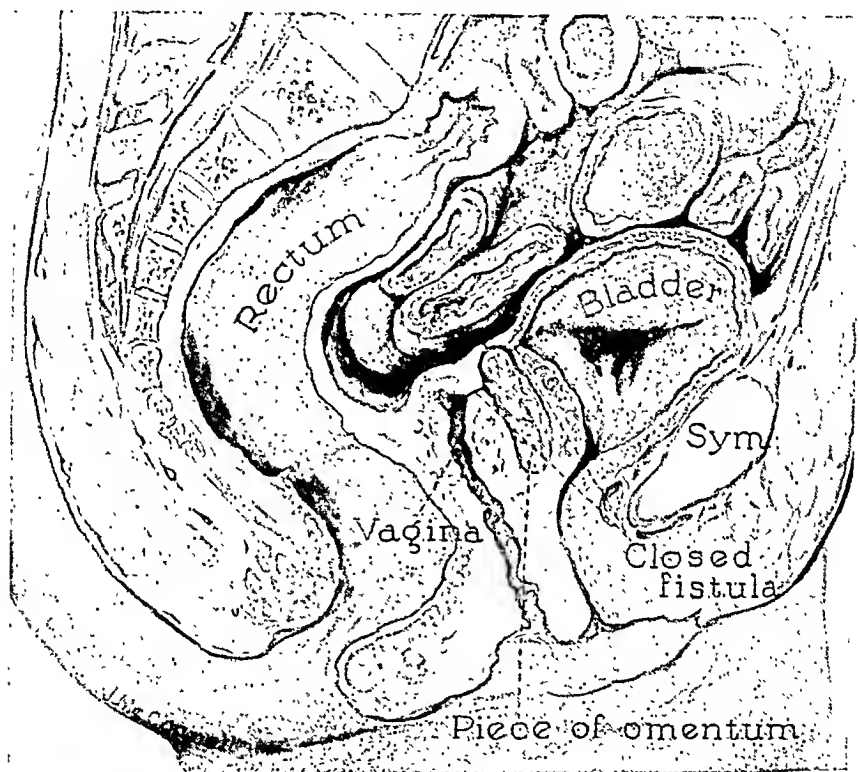


Fig. 2.

In the case which I describe, it was not possible to do this, as the omentum was not long enough to make it possible to draw its lower end into the operative field. Accordingly, a piece, roughly square and about 10 cm. on each side, was excised from the omentum and sutured between the two repaired structures with fine catgut.

In parous women, the vaginal relaxation which is usually present will allow access to the fistula, although the deep incision advocated by Ward may be needed. In exceptional cases, as the one here described, the transperitoneal approach may be useful. If I have occasion to make use of the operation again, I shall have a ureteral catheter passed through the fistulous tract before beginning the operation, in order to facilitate the finding of the fistulous tract.

This patient has remained completely dry since the operation. A Pezzer catheter was left in the bladder for fifteen days. For some time after operation she complained of frequent urination but at no time was there lack of control. This disappeared within two weeks and at present she has complete control of the bladder. She urinates usually once during the night but says that she had done that for years before the operation which was the cause of the fistula. I wish merely to draw attention to an operation which, in occasional cases, may provide

A probe would not pass into the fistula which, evidently, was tortuous. Cystoscopy by Dr. J. I. Farrell disclosed vesical end of fistula at the base of the bladder, to the right of the median line, surrounded by scar tissue which probably followed an attempt at repair.

One week later an attempt was made by Dr. Farrell to close the fistula by passing an electrocoagulating wire through the cystoscope into the fistulous tract, in order to destroy its epithelial lining. Relief for a few days followed this, probably by reason of the edema of the tissue surrounding the fistula, but leakage soon began again. Operation was then decided upon and was carried out as follows:

*Median Laparotomy.*—Separation of extensive adhesions. After slowly dissecting the bladder off the vaginal vault, the fistula was difficult to locate. The bladder

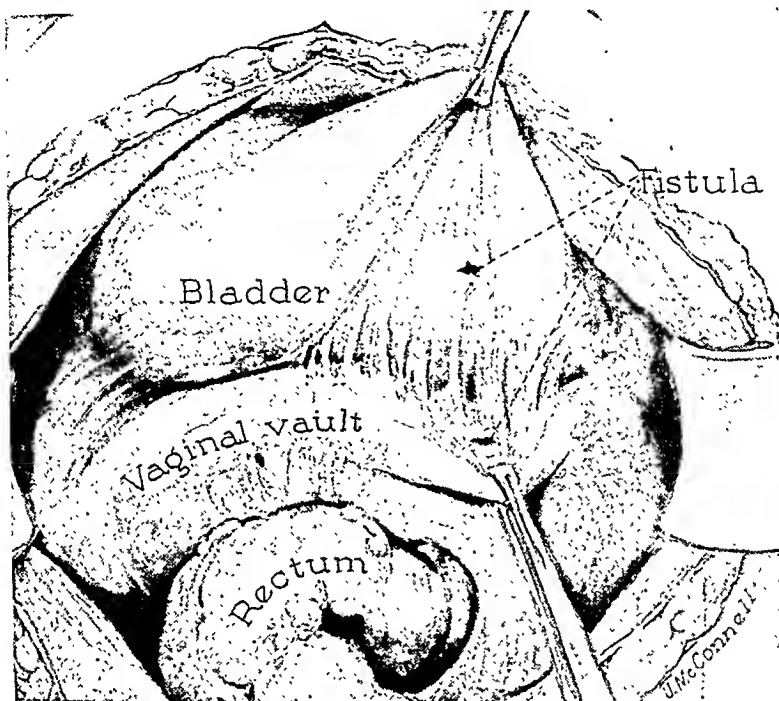


Fig. 1.

was then injected with methyl blue and after further dissection the blue escaped through the fistulous opening. The hole in the bladder and the hole in the vagina were separated and dissection around them was carried out until the bladder could be mobilized. With three interrupted sutures of fine catgut the hole in the bladder was closed and with the second row of sutures this first row was turned in. The vaginal opening was then closed. Omentum could not be brought down to the area of sutures, so a piece was detached and was sutured between the suture lines in the vagina and the bladder, in order to prevent their coming in contact. Penrose drain was carried down to the pelvis. Closure of the abdominal wall by layer sutures of catgut, four stay sutures of braided silk and running silk suture in the skin. One laparotomy pad was introduced but this was removed. A retention catheter was left in the bladder.

My preference, in operating upon fistulas between the vagina and the bladder, is to deal with them from below. In all clinics it has been found possible to manage the great majority by vaginal operation. It is because, in rare cases, especially in elderly nulliparous women, fistulas located at the highest point of the vaginal vault may be difficult to get at even by the method of Ward. I wish to direct attention to this method. In 1881, Trendelenburg suggested the possibility of operating upon inaccessible fistulas in this way, but was successful for the first time in 1888. Legueu, in 1914, described the method of transperitoneal operation for the closure

## FOCAL INFECTIONS IN PREGNANCY\*

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WHEN in 1931, a paper on "Focal Infections in Pregnancy" was written by one of the authors (C. E. G.), it was suggested that, since prenatal care is a form of preventive medicine, one should be as thorough as possible in one's investigation of the pregnant woman. It was contended that the possible role of foci of infection, especially in the teeth and tonsils, was being overlooked. In 1929 one of us (C. E. G.) began to require full-mouth roentgen ray films for all those receiving prenatal care.

The paper<sup>1</sup> published in 1931 was based on 242 cases studied. Among these, 36 patients, or 15 per cent, were found with definite apical infections. Of these 36 patients, 25 had extractions with no resulting abortions. Twelve uneventful tonsillectomies were also reported. The following statement was made at that time, "It is very difficult to demonstrate any benefit from a preventative procedure such as the removal of various foci of infection, but since adopting the procedure of requiring full-mouth x-ray films and examination of the teeth and tonsils, I have had fewer cases of pyelitis, mastitis and toxemia."

In the present study we have attempted to determine whether such a procedure has proved successful in private practice. The paper is based on the study of 843 additional pregnancies occurring in 704 women. The cases previously reported are not included. The roentgen ray report accompanies each record of the 843 pregnancies. One hundred and twenty-five, or 14.8 per cent, disclose the presence of definite apical infection. This agrees closely with the 15 per cent incidence of infection noted in the earlier paper. A study of these 125 pregnancies, where apical infections could be demonstrated, shows that 85 patients had infected teeth extracted during pregnancy. The remaining 40 retained their infection. Twenty-seven additional extractions were done because of excessive decay.

In 36 cases, or 4.27 per cent, tonsillectomies were advised because of apparent foci of infection; 23 tonsillectomies were performed. Six hundred and thirty-two patients showed no apparent evidence of infection in either teeth or tonsils.

### INCIDENCE OF PYELITIS

The literature on pyelitis of pregnancy gives widely diverent figures for the incidence of this complication of pregnancy. Douglass and Laughlin<sup>2</sup> state that pyelitis of pregnancy occurs in about 25 per cent of the cases. They quote Traut with an incidence of 2 per cent, Mussey with 20 per cent, Baird 42.5 per cent, and Emge 7 per cent. McLane<sup>3</sup> in a five-year study at the New York Hospital saw

\*Presented at a meeting of the Chicago Gynecological Society, October 20, 1939.

a means of meeting what may appear to be a very difficult technical problem. The use of the mass of omental fat in order to keep the suture lines in the bladder and the vagina apart I believe is an extremely valuable, if not indispensable, part of the procedure. The great importance of a complete separation of the two suture lines should be emphasized.

### DISCUSSION

DR. JOSEPH L. BAER.—One can do no more than applaud the successful outcome of a difficult operation of this sort which relieves the patient of an intolerable disability. I have two questions in mind. Dr. Danforth intimated that if the omentum had reached the area in which he did the repair, he would have tacked it into that area. Since it did not, he resected a piece of omentum and interposed it between the vagina and the bladder. I wonder if he had this to do again would he not prefer to use a piece of detached omentum rather than anchor the omentum into the true pelvis and thereby set up a train of gastrointestinal symptoms.

Second, if I heard correctly, Dr. Danforth said he used a Pezzer catheter which was left in situ for fifteen days. Our experience is that the longer a catheter is left in situ the more certainly the patient gets some degree of cystitis. If that is true, then much earlier removal of the permanent catheter with catheterization at intervals sufficient to guard against over-distention would do away with the risk of causing a severe postoperative cystitis.

DR. CHANNING W. BARRETT.—It seems to me in the average case that the abdominal approach to a vesicovaginal fistula is impractical. There is only the occasional case in which the smallness of the vagina might make a vesicovaginal fistula difficult to reach.

The best way of closing that bladder is by suture of the bladder wall, and a piece of spongy omentum would be quite unnecessary.

DR. H. O. JONES.—One occasionally sees vesicovaginal fistulas that empty into the vagina many inches away from their origin. I have seen one case in which five different efforts to repair failed.

I would like to ask Dr. Danforth if all these patients are not better if they lie on the abdomen and face during the recovery period after operation.

DR. EUGENE A. EDWARDS.—Is it a wise procedure to transplant omentum into a potentially infected field? I once saw such a transplant become infected. It later came out of the abdominal incision.

DR. W. C. DANFORTH (closing).—In regard to Dr. Baer's question, I was influenced in my desire to use omentum without detaching it by a report by Waltman Walters of the Mayo Clinic. Since in this case it worked out successfully, I should do the same in another case.

As to the catheter, I left it in deliberately longer than we ordinarily do, because I wanted to protect the wound from any distention or pressure. We had to change the catheter a number of times. On one occasion it became quite full of incrustations. When this occurs, the catheter is of little value.

Dr. Barrett spoke about the abdominal route. We only chose this method after considering a closer means of approach. We do not ordinarily adopt this route. I should attack from below under ordinary circumstances. It was a difficult case, because it had been operated upon twice before.

I think in most cases it is wise to use the abdominal position for postoperative care which Dr. Jones spoke of. We employ it usually but in this one we sat the woman up on a back rest because of the abdominal wall which, at first, was drained.



greater than that of apparently normal cases, and their removal should not be a deterring force. We stress the following in regard to the removal of teeth and tonsils in pregnant women:

1. Removal of all foci as early as possible.
2. Some patients gag when being x-rayed. If nausea is already present, a mild sedative is suggested or painting with a weak cocaine solution.
3. It is best not to extract at the time of a menstrual cycle.
4. The patient should remain at home for two or three days following an extraction.
5. Codeine is used for relief of pain rather than anacin or other compounds which contain quinine.
6. There should be no upper respiratory infection at the time.
7. Only local anesthesia should be used for extraction of teeth or tonsillectomy; the risk of general anesthesia is too great. The operator may be forced to hurry, and with tonsillectomy there is danger of lung abscess.
8. If the patient has a severe reaction, she must be put to bed, given a narcotic and proluton or lutein.
9. It is a good general rule to have x-rays made, if possible, by one who does nothing else. The average dentist makes poor pictures, and it costs the patient no more to have them made by a special laboratory. The dentist is usually glad to have a better set of x-rays than he himself can make. The obstetrician is seeking consultation and has a right to send the patient wherever he believes the best results are being obtained.
10. Extractions are better handled by an exodontist.
11. The patient should be told, not asked, to have the teeth or tonsils removed.

#### SUMMARY

1. This study of 843 pregnancies shows that 14.8 per cent of the patients had definitely infected teeth and about 4.27 per cent had tonsils which could be considered harboring foci of infection.

2. The incidence of pyelitis in the entire group was 3.56 per cent, whereas, the incidence was 17.5 per cent where infected teeth were allowed to remain during the pregnancy.

3. The incidence of hypertensive toxemia in the entire group was 3.32 per cent. In the patients with infected teeth it was 5 per cent. In patients with infected tonsils it was 7.6 per cent.

4. The incidence of abortion was 5.6 per cent for the 843 cases. In patients with infected teeth not removed, 20 per cent aborted. In those patients with infected tonsils, 15.4 per cent aborted.

5. The incidence of abortion which could be attributed to the removal of foci was 3.5 per cent for extraction of infected teeth and 4.3 per cent for removal of tonsils. These figures are lower than the incidence for the entire group.

#### CONCLUSIONS

Routine search for and elimination of foci of infection in the teeth and tonsils should be a regular part of prenatal care if patients are to receive the attention due them.

Failure to remove such foci leads to a greater incidence of pyelitis and abortion and a smaller but definite increase in toxemia.

Removal of these foci of infection during pregnancy does not increase the risk of abortion over that normally found.

168 cases of proved pyelitis in a total of 14,000, an incidence of 1.2 per cent. He said that many more cases were studied but were discarded because of insufficient evidence of pyelitis. Kretschmer makes the statement that many cases of pyelitis in pregnancy are overlooked because of the mildness of the symptoms and failure to study the urine carefully.

In this series of 843 pregnancies there were 30, or 3.50 per cent, with urinary tract infection, varying from a definitely infected urine to typical pyelitis with chills, fever, and pain sufficient to warrant bed rest. In the 632 pregnancies with no evidence of foci of infection, the incidence is 3.16 per cent. The 85 pregnancies in which infected teeth had been removed showed an incidence of 2.35 per cent. The 40 pregnancies in which infected teeth were not removed as advised showed an incidence of 17.5 per cent. As far as this small series is concerned, infected tonsils did not seem to be an important factor in the occurrence of pyelitis.

#### INCIDENCE OF HYPERTENSIVE TOXEMIA

Dieckmann and Brown<sup>4</sup> have given an incidence of 7.5 per cent in delivery of toxemic patients in their study of hypertension and pregnancy. In a more recent study of the toxemic patient<sup>5</sup> they have stated that the hospital incidence of non-convulsive toxemia of pregnancy in the United States varies from 0.2 per cent to 29 per cent, an average of 4 per cent. In this study, any patient having a blood pressure of 140 or more, with albumin in the urine, and edema was considered to have toxemia of pregnancy. We make no attempt to classify these cases other than to state that no cases of eclampsia occurred in the group.

In the 843 pregnancies there were 28, or 3.32 per cent, with varying degrees of toxemia. In the 632 patients with no evidence of foci, the incidence was exactly the same. In the 40 patients who had infected teeth remaining, the incidence was 5 per cent. In 13 patients with suspected infected tonsils still present, the incidence was 7.6 per cent. This group of patients is too small to enable us to draw any conclusions from the findings, but these figures would seem to indicate that foci of infection do play at least a small part in the production of toxemia of pregnancy.

#### INCIDENCE OF ABORTION

In a previous paper<sup>6</sup> we reported an incidence of abortion of 7.9 per cent among our private patients. By abortion we mean the loss of the pregnancy up to the twenty-eighth week. This paper considered all cases of abortion, and, since many of these were first seen at the time the bleeding started, there were no records to indicate the presence of foci of infection. Thus, many cases of abortion could not be used in this study and the incidence of abortion in this series of 843 pregnancies is only 5.6 per cent for the entire group and 4.43 per cent for the 632 patients, with no evidence of foci in the teeth or tonsils. The incidence of abortion in the 85 patients in whom infected teeth were removed was 4.7 per cent, and in the group of 40 patients where the infected teeth were not removed, it was 20 per cent, an increase almost five times as high. In only 3 patients was the extraction of the teeth considered a direct factor in causing the abortion, an incidence of 3.5 per cent. These cases will be given in detail later.

The 13 patients where the tonsils were considered infected gave an incidence of 15.4 per cent for abortion. Of the 23 tonsillectomies done, 3 patients had the pregnancy terminated by abortion, but careful study of these records seems to indicate that in only 1 patient was the operation a definite factor in producing the abortion. Allowing for this, we have an incidence of 4.3 per cent for abortion resulting from tonsillectomy. Details on these cases are given at the end of the paper.

#### DISCUSSION

We are convinced that foci of infection in the teeth and tonsils should be carefully searched out and removed as soon as found. Failure to remove these foci of infection seems to increase the incidence of abortion and perhaps is a factor tending to increase pyelitis. The incidence of abortion resulting from extraction of teeth or removal of tonsils is no

## MISSED LABOR\*

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IT IS the extreme rarity of this type of case together with the many unusual features presented by this case, that prompted its reporting. This term was first used to describe the condition of retention of a full-term, or near full-term, dead fetus within the uterus, beyond the expected date of confinement; it was so used by Oldham<sup>1</sup> in 1847, in reporting a case of a multiparous patient who died three months beyond term carrying the remnants of a full-term fetus; for the two and one-half months preceding her death, portions of the fetus had been removed at several sittings, through the cervix, and just before death it had ulcerated through the uterus into the peritoneal cavity and into the bladder. Since that time the term missed abortion has been applied to a similar retention of a nonviable fetus; much literature has appeared on this subject. While there are many similarities between these two conditions, they would seem from a study of the few cases of missed labor reported in the literature to present sufficient differences to consider them separately.

While most likely the reason for the failure of the uterus to expel its contents is to be found in some endocrinal deficiency, there have been many other reasons offered, such as rigid cervix, cancer, scars, diseased uterus, myomas, muscular degeneration, and cornual pregnancy. As one reviews the case to be presented and the cases noted in the literature, one wonders whether aside from cornual pregnancy, and possibly cancer and fibroids, all the remaining conditions are not part and parcel of the condition of missed labor. Peter<sup>2</sup> mentions a case associated with fibroids that was retained for twelve years (the patient having refused operation), and the finding at post mortem of a mummified full-term fetus in the uterine cavity. Arnold<sup>3</sup> in his discussion of missed abortion mentions the report of a case in "Osservatore Medico" (1834) of a woman who thought herself pregnant for fifty-one years and at post mortem a desiccated full-term child was found in the uterus. Both Williams<sup>4</sup> and DeLee<sup>5</sup> cite the cases of Menzies and Hennig, in which the fetus was retained for 280 and 210 days, respectively, after full term. Lichtwardt<sup>6</sup> reported a case that retained the skeleton of an eight-month-old fetus for a period of twenty-six months, during which 2 fistulas were formed between the fundus of the uterus and the transverse colon, and finally a fistula between the uterus and the anterior abdominal wall. Lakhoti<sup>7</sup> reported the case of a twenty-seven-year-old woman pregnant ten months, who twenty days previously had had a watery discharge from the vagina and finally ulcerated through the abdominal wall and discharged portions of the fetus; this opening communicated with the vagina. Hughes<sup>8</sup> reported a case two months after the expected date of confinement and ten weeks after the death of the fetus with failure of pituitrin to induce labor and termination by cesarean section. Smith<sup>9</sup> reported a similar case of a full-term pregnancy ten weeks after the expected date of confinement and six weeks after the death of the fetus, terminated by cesarean section with the diagnosis between missed labor and abdominal pregnancy in doubt. Potter<sup>10</sup> reported a case that had gone two months after the expected date of confinement and there were cessation of fetal movements and no apparent cervical opening; delivery was effected by cesarean section, a placenta accreta being then found together with many adhesions of the uterus to intestines, omentum, and abdominal wall; these adhesions were thought to have been caused by degeneration of fibroids during pregnancy; they were so extensive as to make hysterectomy impossible.

This condition would appear compatible with good health if no infection sets in, the only complaint then being the difficulty of carrying the large dead weight in the abdomen. From time to time pains of a parturient character may set in, but will subside, as will any vaginal bleeding that may occur. The diagnosis thus offers

\*Read at a meeting of The Brooklyn Gynecological Society, October 6, 1939.

## PROTOCOLS

## Abortion cases after tooth extraction:

CASE 73.—Mrs. H. L. H., aged 32 years, para ii, last menstrual period Feb. 28, 1930, was first seen on May 2, 1930. She had one infected tooth extracted at the end of May and a severe reaction followed. The patient was in hospital on June 5 and 6 with pelvic pain and spotting. On July 7 she was again hospitalized for spotting and pain. On July 21 she expelled a four-and-one-half-months' fetus and placenta.

CASE 87.—Mrs. M. M. Z., aged 29 years, para iii, last menstrual period Feb. 1, 1930, was seen on March 11 and then not until May 2, during which time she had a severe left antrum infection and chronic sore throat. On May 26 it was noted that the patient had had an infected upper left first molar extracted and a tonsillectomy was advised. Note June 24 reads, "Missed abortion 3 months." Pregnancy test on July 1, 1930 was negative. The uterus finally was evacuated Aug. 14, 1930.

CASE 680.—Mrs. J. R., aged 31 years, para i, last menstrual period May 5, 1936, was first seen June 20, and she had had six teeth extracted shortly before this, some of which were infected. On June 29, patient had bloody show and aborted July 6, 1936.

## Abortion cases after tonsillectomy:

CASE 223.—Mrs. A. J. W., aged 29 years, para ii, last menstrual period March 17, 1934, was first seen April 24, and tonsillectomy was advised. Tonsillectomy was done on May 1, 1934, at St. Luke's Hospital. She was seen in the office May 15 and everything was apparently normal. On May 30 she reported spotting without pain. On June 1 profuse bleeding began; patient was sent to the hospital and dilatation and curettage were done.

CASE 278.—Mrs. G. W. P., aged 35 years, para iii, last menstrual period Feb. 15, 1931, was first seen May 26, and tonsillectomy was advised. She also had possible areas of infection at the apices of two teeth. On June 26 the tonsils were removed. She felt life at end of June and when seen on subsequent visits, July 7, 27, and August 17, everything apparently was normal. On August 24, the patient called and reported that she had felt no fetal movements for four days. She was seen on August 31 and no fetal heart tones were heard. She delivered October 2 a macerated fetus from four to five months of age.

CASE 14.—Mrs. W. D. N., aged 32 years, para i, gravida iv, last menstrual period Sept. 23, 1929, was first seen Dec. 9, 1929. Tonsillectomy had been performed on Nov. 29, 1929. When seen on Jan. 3, 1930, everything seemed normal. On Jan. 19, 1930 patient was having contractions and she aborted Feb. 4, 1930.

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Fusimori, H., and Mizuno, K.: *Vaginal Porro Operations*, *Jap. J. Obst. & Gynec.* 22: 119, 1939.

At full term, in order to interrupt pregnancy and produce sterilization at the same time, either a Porro operation is performed after emptying the uterus, or the tubes are ligated following the removal of the baby. In cases before the fourth month, the authors prefer to perform a Porro operation through the vagina. The pregnant uterus is removed supracervically. Since 1934 the authors have done 32 of these operations and with good results in all. Spinal anesthesia was used in these cases. In two instances, stump abscesses resulted, but these were cured by vaginal puncture.

J. P. GREENHILL.

The patient was discharged on July 15, 1938 after an uneventful stay in the hospital; she was cautioned against intercourse and advised to return immediately if membranes ruptured.

Patient was re-admitted to hospital on Aug. 2, 1938 because of vaginal staining and abdominal cramps. She stated she felt fetal movements. The presentation was now more oblique than transverse and the fetal heart could not be heard. She was given castor oil and an enema, but these failed to initiate labor. X-ray examination on Aug. 3, 1938 showed further overlapping of the fetal skull bones. Glucose tolerance test on Aug. 6, 1938 showed a more normal response. Patient was discharged on Aug. 6, 1938 to return to the prenatal clinic.

Blood pressure and urine examinations on September 1, October 2, October 10, and November 14 were normal. A few days after the September 1 visit she had some bright red staining which promptly subsided. At this same visit a presenting part was noted in the pelvis, believed to be vertex; and the fundus measured 33 cm. She stained again on October 7 to 10. During all this time patient stated she felt life and that her abdomen was growing. X-ray on October 1 demonstrated further overlapping of fetal skull bones and more marked angulation of the spine. Vaginal examination on November 14 revealed a cervix about 0.5 inch long, soft, closed, and vertex presenting. She noted some brown vaginal staining for several days in the beginning of November.

Patient was again admitted to the hospital on November 21, 1938. At this time no secretion was noted in the breasts. The fundus measured 32 cm. On vaginal examination the cervix was noted to be firm, about 1 inch long and closed; also an indefinite bulging on left side of lower uterine segment was noted. The pregnancy appeared to be intrauterine, although no definite uterine contractions could be elicited. General condition of the patient was excellent.

In spite of the fact that it was felt that the pregnancy was probably intrauterine, steps were considered to establish this beyond question of a doubt. Digital examination and sounding were decided upon rather than lipiodol injection, but were deferred until endocrinologic study could be completed. On November 27 a low twenty-four-hour output of estrin (65 R.U.) was reported together with a strongly positive prolan. Vaginal smear on November 28 showed 1-plus estrin effect and pH was 7.0. Patient was then given 300,000 I.U. of progynon B every eight hours for a total of 900,000 I.U. plus 2 mm. of pituitrin every two hours for 6 doses without producing any uterine contractions. After the second dose of progynon, pH of vagina was 5.0 and smear showed 4-plus estrin effect. On the day following the completion of the administration of the estrogens, the cervix was found to be shortened, considerably effaced and admitting a tip of a finger. A further course of pituitrin (2 c.c. every hour for 6 doses) was given but with no effect. On November 22 and 29 Aschheim-Zondek tests were reported negative.

On Dec. 1, 1938, almost five months after the expected date of confinement, the patient was taken to the delivery room and examination done under anesthesia. The cervix was found to be 1.5 inches long, rigid, external os just admitting a small dilator. In the left fornix a head could be felt which was apparently intrauterine. After dilating the cervix with Hegar dilators up to No. 18, the index finger was forced through the internal os and the vertex was felt to the left with the aid of pressure from above. A dense piece of tissue intervened between the head and the examining finger. A sound passed very easily to the right without meeting any obstruction.

It was now decided to observe the patient for about one week and if the temperature remained normal, to perform laparotomy then.

The following day (December 2) her temperature rose to 102.8° F. and some spasticity and tenderness of the uterus were noted. On December 3 the temperature was similarly elevated and the tenderness was more marked in the R.U.Q. and R.L.Q. over the uterus with definite rebound tenderness. The white blood count was 25,000 with 90 per cent polymorphonuclears. On this day she passed a large worm (*Ascaris lumbricoides*) in the stool. A blood culture was taken and sulfanilamide medication was started. On December 4 moderate cyanosis of the lips was noted. She was given intravenous glucose in addition to the sulfanilamide. On this night crepitation over the right side of the uterus was noted, about 4 inches in diameter

no difficulty except in its differentiation from abdominal pregnancy where the proximity of the small parts to the examining abdominal hand may be of help in distinguishing; sounding the uterus or injection of an opaque medium into the uterus may be necessary to distinguish the two. It would seem to the author relatively unimportant to make this differentiation at the expense of the danger of infection since the treatment for abdominal pregnancy and for missed labor if it has progressed for any length of time should be laparotomy. Williams mentions that he has had some success with bougies and bags, but does not state how long after the expected date of confinement intervention was undertaken; possibly if early these may be successful, but if it is done late, the torpidity of the uterine muscle is such that one may use all sorts of local irritants without evoking any pains. An examination of the uterine wall in the case reported, which was of paper thinness, would convince one that labor is impossible. It is even doubtful if delivery from below should be attempted at all because of the danger of producing an infected field if unsuccessful. Further, because of the danger of ulceration into neighboring cavities, the uterus should be emptied as soon as the diagnosis of missed labor is made.

#### CASE REPORT

J. O., aged 25 years, housewife, born in United States, married three years, had had no previous pregnancies. Family history was negative except for the fact that her mother had had twins. Previous medical and surgical history were negative. Menses commenced at 11, occurred every twenty-eight days and lasted four days; flow was moderate and there was no pain associated with periods. Her last menstrual period occurred Oct. 2, 1937, making the expected date of confinement July 9, 1938.

During the first five months of the pregnancy, she had had vaginal bleeding and upon the advice of her physician was in bed most of this period. Since then no further bleeding had occurred. The patient stated that she first felt life in December. Prenatal course, including blood pressure and urine, was further uneventful (except for a slight amount of reducing substance in the urine) until two weeks prior to her hospital admission (July 10, 1938) when fetal movements ceased. Her physician at this time diagnosed a transverse presentation. Because of the abnormal presentation and the death of the fetus and the absence of labor, he advised hospitalization. She was admitted to the ward service on July 10, 1938, with the additional history that she had a brown vaginal discharge since the previous day.

On examination her temperature, pulse, and respirations were normal. Eyes, ears, nose, throat, heart, and lungs were normal. The breasts were noted to contain colostrum. The abdomen revealed a full-term fetal ovoid in transverse presentation with the head in L.L.Q., breech on right and back anterior; the fetal heart was not heard, and there was some tenderness in the R. L. Q. On rectal examination the cervix was thick and had no dilatation; no presenting part was felt. Vaginal examination revealed a long soft cervix admitting 1 finger, membranes intact, no presenting part in pelvis, some small parts felt through lower uterine segment; the pelvis was normal.

X-ray examination on July 11, 1938 corroborated the transverse presentation and demonstrated marked angulation of the fetal spine. On July 13, 1938 the x-ray further demonstrated some overlapping of the fetal skull bones.

Glucose tolerance test on July 12, 1938 was as follows:

8:00 A.M.	Blood	90 mg. %	Urine	neg.
8:50 A.M.		191		0.008 Gm.
9:45 A.M.		255		0.45
10:45 A.M.		234		0.48

The response was that of a latent diabetic.

July 10, 1938, Urine, sp. gr. 1.020; reaction acid; negative sugar, albumin, acetone and microscopic.

July 11, 1938, R.B.C., 4,500,000, Hg, 78 per cent; W.B.C., 10,000; polymorphonuclears, 70 per cent; lymphocytes, 30 per cent.

July 12, 1938, Blood urea nitrogen, 9.7; uric acid, 3.6.

July 12, 1938, Kline test, negative.

brown exudate which was dry and gritty. There was very little bleeding from the uterus which was paperlike in thinness.

*Procedure.*—Adhesions binding the uterus were freed. The uterus was mobilized and brought out on the abdominal wall. Posteriorly the sanguineous pus could be seen welling up into the wound. The abdominal cavity was walled off with tapes and the uterus was opened. Macerated fetus was removed; cord cut, placenta and membranes removed with difficulty, some of the latter remaining behind adherent to the uterus. The uterus was now a thinned-out sac and collapsed with no bleeding. As much of the wall of the uterus was removed as possible, more extensive excision being restricted because of the high bladder and the adherent sigmoid. All bleeding points were ligated. Bleeding points of omentum freed from the uterus were tied. The remaining uterine wall was sutured at the angles. Iodoform strips were placed in the remaining uterine cavity. The stump of the uterus now was exteriorized by suturing the wall of the uterus to the abdominal parietes.



Fig. 2.

Fig. 2.—Section through entire thickness of wall of uterus with adherent portion of placenta, demonstrating also exudate on peritoneal surface. ( $\times 60$ .)



Fig. 3.

Fig. 3.—Section through placenta demonstrating ghosts of chorionic villi and calcification. ( $\times 60$ .)

Through-and-through sutures of interrupted chromic catgut No. 2 were used to close the abdomen, including the peritoneum, muscle, and fascia. Two cigarette drains were placed in the cul-de-sac and 2 in front of the uterine stump. Skin was closed with interrupted black silk sutures.

Patient received 500 c.c. of citrated blood and intravenous glucose.

Patient's condition continued grave, temperature ranging between 103° and 106° F. Abdominal distention was combated with Wangenstein apparatus. Sulfanilamide, serum, and blood transfusions continued. Slight icterus was noted on second day postoperative; but condition at this time appeared slightly improved. On third day postoperative patient became disoriented and condition grew progressively worse, and she died on the fifth postoperative day.

*Pathologic Reports.*—Microscopic examination of the placenta showed acellular tissue in which ghosts of former chorionic villi and decidual cells could be seen. Scattered through it were numerous small and large deposits of calcium.

and to the right and above the umbilicus. Gas bacillus serum was immediately administered and transfusion ordered. The following morning (December 5) with the temperature 103.8° F., there was a resonant percussion note over the entire uterus. Patient was transferred to the gynecological ward on the service of Drs. Schwartz and Wolfe, where the cervix was exposed and found to be swollen, edematous, and covered by a shaggy exudate. The os was found and admitted a small dilator; internal os could not be passed and was not forced. Applicators were used to obtain cultures. X-ray examination at this time demonstrated air around the fetus anteriorly and superiorly within the uterine cavity; no air could be demonstrated in the soft tissues of the abdominal wall. On December 6 with her general condition becoming progressively poorer in spite of sulfanilamide and gas bacillus serum, and definite evidence of spread of the crepitant area of the uterus, exploration was decided upon.

*Operation.*—The field was blocked with 1 per cent novocaine and a right pararectus incision made. As the parietal peritoneum was opened one could hear gas escaping. No evidence of pus or generalized peritonitis was observed. The right upper portion of the uterus was adherent to the abdominal wall. As these adhesions were

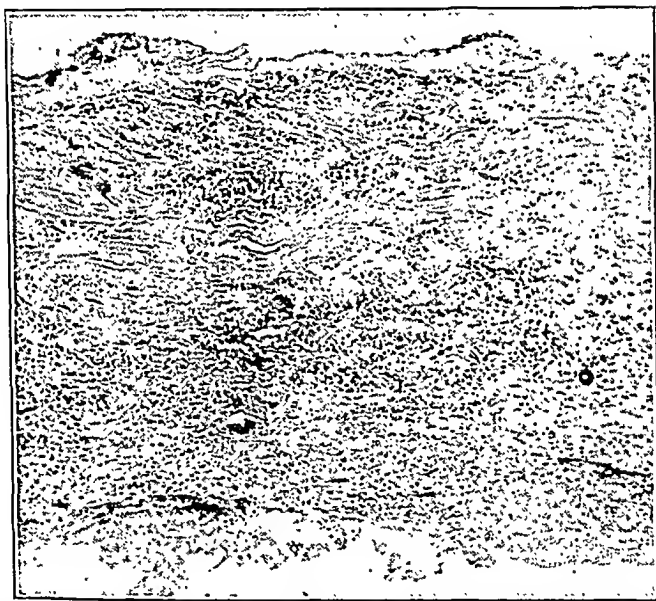


Fig. 1.—Section through entire thickness of uterine wall, demonstrating extreme thinness, necrosis of muscle fibers, and dense cellular infiltration. ( $\times 200$ .)

freed, escaping gas was heard. The anterior bladder reflection was attached high up to the fundus by additional adhesive bands. Adhesions were noted binding the uterus to both lateral pelvic walls. These adhesions appeared to be evidence of an older infection. Posteriorly on the left the sigmoid was intimately adherent to the body of the uterus. The omentum was found adherent posteriorly to the uterus, and a perforation (size of a dime) of the uterus was noticed in the right posterolateral portion of the lower uterine segment. About 200 c.c. of sanguinopurulent fluid escaped from the cul-de-sac of Douglas as this area was explored. Just superior to this and on the posterior surface close to the fundus, a circumscribed area of softening was noted in the wall of the uterus; omentum was plastered over this point in an effort to seal it off. The uterus itself was thin walled, of a pinkish white hue, and gas was felt in its cavity. When the uterus was opened no fluid was obtained. An oversized macerated fetus, measuring 57 cm., was found undergoing decomposition. Necrotic tissue of a fecallike appearance was found in the cavity. When the uterus was opened, gas escaped. The placenta and membranes were firmly adherent to the uterine wall. The endometrium was covered by a light



## BIPARTITE UTERUS\*

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WE DESIRE to report an unusual case which has recently been seen on our service.

In May, 1939, a 23-year-old white woman, tripara, entered the Evanston Hospital in labor. The labor was normal and rapid. A child weighing 3,540 Gm. was delivered spontaneously. The anus was imperforate; no external urethral orifice could be seen. What appeared to be the clitoris was much larger than normal. The infant was cyanotic at birth, and later the skin had a dusky hue. Fourteen hours after delivery the abdomen became distended. On the following morning fluid trickled from a pin-point opening in the external genitalia. From the second day on meconium-like material was regurgitated at frequent intervals. Watery fluid, apparently urine, was observed coming from the umbilical cord.



Fig. 1.—Roentgenogram taken with the patient in an inverted position. Arrows point to two fluid levels in the bipartite uterus. The third, fourth, fifth sacral vertebrae and coccyx are absent.

A roentgenographic examination on the day of delivery disclosed gas in the bowel at the level of the first and second lumbar vertebrae, which indicated gas in the small bowel, none having passed into the sigmoid and rectum. The nature of the obstruction could not be determined. A second roentgenologic examination (Fig. 1) two days after birth revealed a pocket of gas over two fluid levels in the true pelvis and lower abdomen. This was interpreted as gas in a hollow viscus, probably bladder. The possibility of the gas being in a distended loop of bowel was also considered.

The signs of obstruction and abdominal distention continued. Surgical intervention appeared useless. Death occurred on the fifth day after birth.

\*Presented at a meeting of the Chicago Gynecological Society, October 20, 1939.

Preparation from the wall of the uterus showed at one end a fibrinopurulent exudate with clumps of purple-blue staining material adherent to the wall. Here there were occasional papillary stalks covered with cylindrical cells. The wall itself was thin, composed of loose fibromuscular tissue infiltrated by many polymorphonuclear leucocytes, eosinophiles, small round cells, and large mononuclear cells. In the deeper portions, the tissue was necrotic, acellular, and contained numerous small and large deposits of calcium. Another preparation showed the endometrial surface covered by cylindrical cells and in places attached to it was a fibrinopurulent exudate; within the wall the tissue was loose with numerous distended thin-walled vessels filled with polymorphonuclear leucocytes, and throughout a dense infiltration by similar cells.

Livers from rabbits injected with cervical swab were compatible with that seen in gas bacillus infection.

December 8, Total sulfanilamide, 8.7 mg. %; free sulfanilamide, 7.5 mg. %

December 9, Total sulfanilamide, 8.3 mg. %; free sulfanilamide, 7.6 mg. %  
Icteric index, 34.6

Blood chlorides, 400 mg. %.

December 6, Culture of peritoneal fluid obtained at operation, *B. welchii*.

R.B.C., 3,850,000; Hg, 81%; W.B.C., 28,200, polys 82%

December 8, R.B.C., 4,240,000; Hg, 81% W.B.C., 15,000, polys 82%

December 10, R.B.C., 2,960,000; Hg, 59%; W.B.C., 7,200, polys 80%

#### SUMMARY

1. The rarity of the condition presented is noted.
2. Cases reported in the literature are briefly reviewed.
3. There appears to be an association of abdominal adhesions and ulcerations into neighboring cavities in cases of missed labor of some duration, especially in the presence of infection.
4. The uterus should be emptied as soon as the condition is diagnosed.
5. The route should be abdominal because of the difficulty in differentiating abdominal pregnancy, and because if attempts (other than medical) at induction are unsuccessful, infection may ensue.
6. A case is presented that carried five months beyond the expected date of confinement with the patient remaining in good health except for somewhat regular occurrence of slight abdominal cramps and some vaginal staining; at the end of five months, the uterus was accidentally perforated by a uterine sound introduced to help establish the diagnosis of an intrauterine pregnancy, with introduction of a *B. welchii* infection and death of the patient in spite of emptying of the uterus, sulfanilamide, and gas bacillus serum.
7. The thinness and necrosis of the uterine musculature is demonstrated.
8. Some endocrinologic studies of this case are presented.

I wish to thank Drs. Schwartz, Blum and Wolfe for the privilege of reporting this case.

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140 EIGHTH AVENUE

It measured 14 cm. from apex to base. The anteroposterior diameter was 12 cm.; the greatest transverse diameter was 13 cm. The fundus of the uterus presented a median anteroposterior shallow depression which marked the position of the internal sagittal septum of the uterus. Each lateral aspect of the fundus presented an elevated mound, representing the cornu from which passed an infantile Fallopian tube 42 mm. long. A narrow, flat infantile ovary, 27 by 8 by 2 mm., was located just posterior to the Fallopian tube. The adnexa hugged the convexity of the lateral margins of the distended uterus. The uterine ligaments were either absent, distorted, or grossly obliterated. The anterior ligaments were absent. The intimate relation of the urinary bladder, to be described, and the ventral uterine wall precluded the possible formation of the vesicouterine excavation. The absent vagina and an incompletely developed rectum explained the failure of development of the rectovaginal folds and the lack of formation of the posterior ligaments. The rectouterine folds and pouch of Douglas were

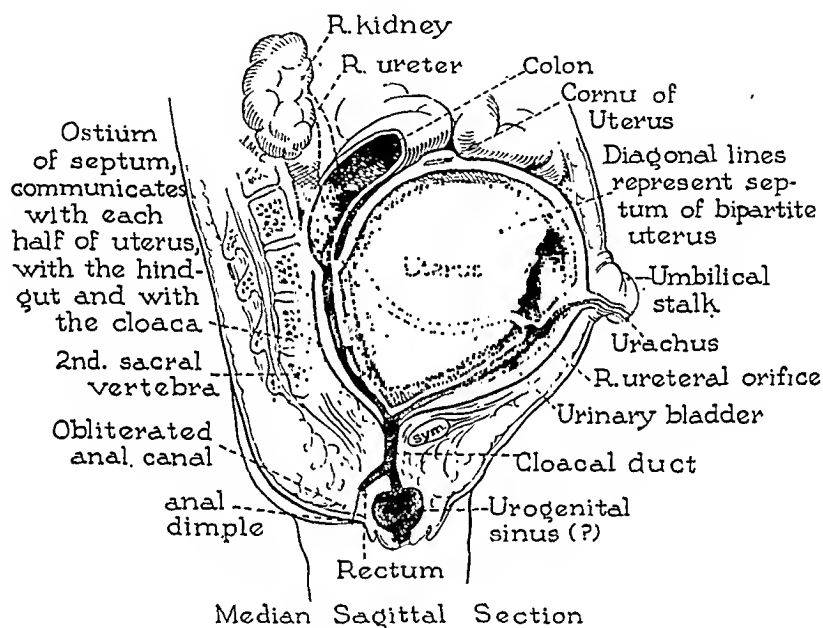


Fig. 3.—Semidiagrammatic median sagittal section of lower abdomen and pelvis.

absent for similar reasons. The abdominal parietal peritoneum formed a short angle of reflection as it passed over the uterus and formed two delicate layers to enclose the Fallopian tubes, the ovaries and their ligaments, and associated vessels and nerves. The ascension of the distended uterus and attached urinary bladder obliterated a pelvic-peritoneal cavity. The round ligaments passed over the distended uterus and veered ventralward.

The stretched walls of the body of the uterus were 3 to 4 mm. thick. The wall at the cornu was 10 to 12 mm. thick. A sagittal partition, 2 mm. thick, divided the uterus. Each half was almost filled with a dark yellow, turbid fluid (urine and fecal material). An oval ostium, 6 mm. in its vertical diameter, located in the middorsal margin of the septum, formed a communication between each half of the uterus and a tubular structure enclosed within the dorsal margin of the septum.

The colon entered the superior surface of the uterus to become enclosed in the dorsal margin of the uterine septum. The lumen of the distended large bowel was reduced to 3 mm. in diameter at its point of entrance into the uterine septum. The bowel then abruptly increased to a diameter of 10 mm., passed 4 cm. caudad in the septum, at which point its lumen again became reduced to 5 mm., where it communicated with each half of the uterine cavity through the above-described septal ostium. It then continued as a narrow tubular structure or persistent "cloacal" canal to communicate with the internal meatus of the urinary bladder just beneath the symphysis, 3 cm. below the septal ostium.

The necropsy was performed four and one-half hours after death. Only the pertinent findings are reported. The body of the full-term female infant weighed 2,990 Gm. It was 45 cm. long. The thin, glistening skin was stretched tightly over the markedly distended globoid abdomen. Yellow, turbid fluid escaped from the encrusted umbilical stump. The anus was absent; in its place was a triangular-shaped bulge of skin containing a central anal dimple. The vagina was absent. The external genitalia were formed by two lateral folds, 25 mm. long, 11 mm. wide, and 15 mm. high. Between them was a longitudinal fold, covered with skin, 15 mm. long, 5 mm. wide, and 10 mm. high. Its cephalic pole was covered with a small cap of skin. The only external opening present was a 2 mm.

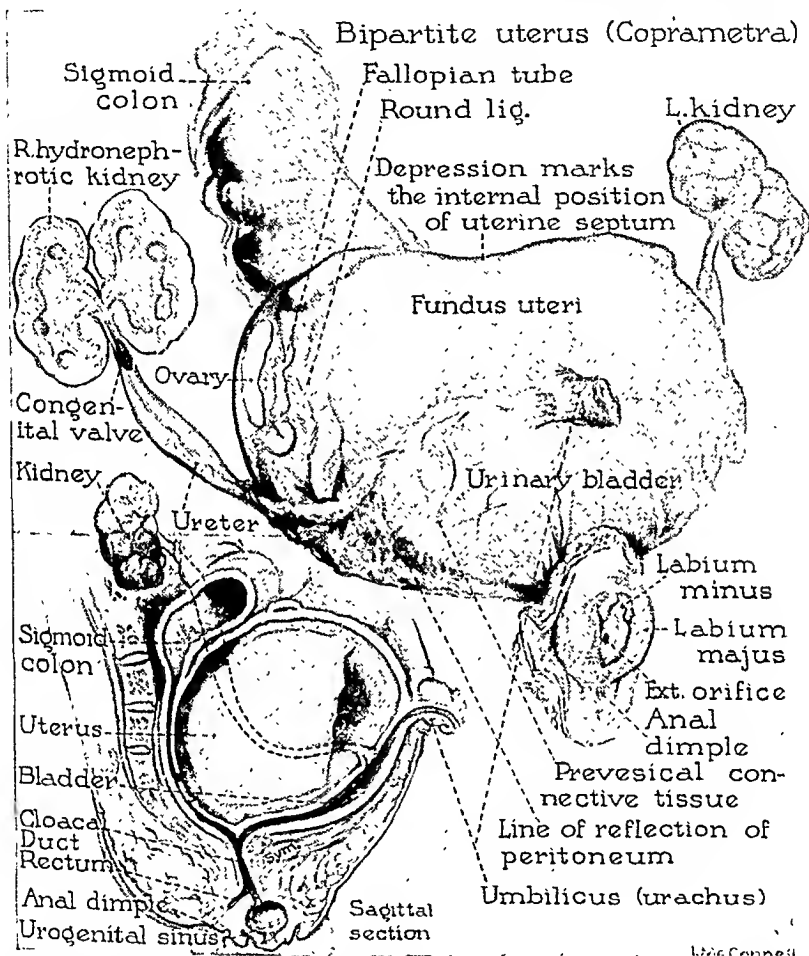


Fig. 2.—Ventral view of sigmoid colon, genitourinary structures, and attached external genitalia and anal region. The smaller drawing is a reconstructed semidiagrammatic sagittal view.

orifice in the midportion of the central longitudinal fold to the right of the midline. A turbid, dark yellow fluid escaped from this orifice when pressure was applied to the abdomen. No other gross external abnormalities were seen.

Upon opening the body cavities, the diaphragm was found elevated. The heart, aorta, and thymus were normal. The compressed lungs were dark red, mottled purple, subcrepitant, and somewhat meaty in consistency, although they floated in water.

Striking anomalies were found in the urogenital organs (Figs. 2 and 3). All but the upper third of the abdominal cavity was occupied by a distended, thin-walled, cystic uterus, adnexa, and urinary bladder, arising from the pelvis. The top of the uterus was 10.5 cm. above the symphysis pubis. The uterus was roughly pyramidal in shape; its base had assumed a cephalic and its apex a caudal position.

and caudal extremities. Only the urinary bladder developed from the vesico-urethral anlage. The urachus did not lose its connection with the umbilicus. The corresponding dorsal region of the cloaca became constricted and elongated to form a narrow rectal tube whose cranial extremity, continuous with the colon, became enclosed between the medial walls of the approximated caudal extremities of the paired Müllerian ducts (uterine septum). The midportion of the cloaca, which failed to undergo division, remained as a cloacal duct. It became elongated and constricted. The caudal extremity of the common cloaca became separated to form a dorsal rectum and ventral urogenital sinus. The clitoris and vaginal vestibule failed to develop. The slender cord of tissue connecting the blind end of the rectum to the skin at the site of the imperforate anus may have been an atretic proctodeum or obliterated anal canal. Normally the anal orifice is formed by the rupture of the dorsal cloacal membrane at the seventh week.

The longitudinal cranial portion of the paired Müllerian ducts developed normally into the Fallopian tubes. From the middle transverse portion developed the uterine fundus and corpus. A sagittal uterine septum persisted because the united uterine primordia failed to fuse. The caudal extremity of the hind-gut and the cranial portion of the rectum were enclosed in the dorsal margin of the merged medial walls of the uterine anlage. The ostium in the dorsal margin of the uterine septum that communicated with the hind-gut probably represented the earlier communication between the Müllerian ducts and the urogenital sinus, which normally occurs about the middle of fetal life. The absent uterine cervix and vagina may be explained by agenesis of the uterovaginal primordium.

The so-called "ureteral valves" present in the upper portion of each ureter are considered to be duplications of the ureteral mucosa. In this case the valves and the compression of the ureters caused a moderate bilateral hydroureteropyelonephrosis. According to H. Young, Wölfer found valvular formations in 20 of 100 newborn children and Motzfeld attributed 9 of 21 causes of hydro-nephrosis to ureteral valves. Englisch observed ureteral valves in human embryos of four months.

#### SUMMARY

The necropsy of a five-day-old, full-term female infant exhibited the following abnormalities of the urogenital system: Bipartite uterus; absent cervix, urethra, vagina, and clitoris; persistent cloacal duct, caudal urogenital sinus, urachus; an imperforate anus and obliterated anal canal. The hind-gut and the cranial portion of the rectum were enclosed in the dorsal margin of the uterine septum. An opening in the dorsal margin of the uterine septum, at the level of the junction of the colon and rectum, formed a communication common to the bowel and each half of the uterine cavity. The thin-walled corpus uteri was distended with feculent fluid (coprametra). These congenital defects are explained by incomplete division of the cloaca, failure of fusion of the midportion of the primordium; agenesis of the uterovaginal, urethral, and phallic anlage. Pressure on the caudal extremity and the presence of a "ureteral valve" in the cranial third of each ureter caused a bilateral hydroureteropyelonephrosis. Absence of the last three sacral vertebrae and the coccyx was due to agenesis of the corresponding sclerotomes. The third, fourth, fifth sacral and coccygeal nerves were absent. Pulmonary atelectasis, congestion, edema, focal hemorrhages, and pneumonitis were terminal.

The bipartite uterus, communicating with the dorsal gut and filled with fluid and gas, accounted for the double fluid level seen in the roentgenogram taken on the second day.

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The flattened, triangular-shaped urinary bladder was intimately attached to the convex ventral uterine wall, from the level of the umbilicus above to the level of the symphysis below. It was 6 cm. long. The transverse diameter of the fundus was 2 cm. The bladder tapered from above downward. A patent urachus passed from the fundus of the bladder through the umbilical stalk. Each ureter entered the superior lateral border of the urinary bladder. The lower extremity of the bladder had an internal meatus 4 mm. in diameter, which communicated just beneath the symphysis pubis with the "cloacal" canal. The canal from the internal meatus of the urinary bladder to the external opening was 35 mm. long. Twenty-three millimeters distal to the former, a blind tubular rectum, 6 mm. long and 1 mm. wide, took its origin from the posterior wall of the "cloaca" and passed dorsocaudad to end 5 mm. from the anal dimple. A slender, white, glistening cord of tissue connected the blind end of the rectum to the skin of the anal dimple. Five millimeters distal to the origin of the blind rectum the "cloacal" canal presented a spherical outpouching 15 mm. in diameter, which may be considered a persistent urogenital sinus. The distal border of the "urogenital sinus" was 2 mm. from the external opening of the "cloaca."

The kidneys were in the normal position. The ureters coursed dorsoventrad over the cystic uterus to enter the bladder. The right kidney measured 50 by 30 by 14 mm. Surfaces made by sectioning displayed a distinct cortico-medullary differentiation. The pale cortex was 2 mm. thick; the pink gray medulla was 4 to 6 mm. thick. The circumference of the ureteropelvic junction was 5 mm. Ten millimeters below the junction a fold of mucosa formed a semilunar valve. The circumference of the ureter above the valve was 10 mm. and below, 22 mm. It contained turbid urine and the smooth mucosa was white.

The left kidney was 53 by 25 by 14 mm. It resembled the right. The circumference of the ureteropelvic junction was 6 mm. Fifteen millimeters below the junction the ureter contained a semilunar valve similar to the right. The circumference above the valve was 6 mm. and below, 20 mm. The ureter was also filled with turbid urine and the mucosa was smooth and white.

The third, fourth, and fifth sacral vertebrae and the coccyx were absent. The third, fourth, and fifth sacral and coccygeal nerves were absent. The spinal cord and brain were not examined.

Histologic observations of hematoxylin and eosin-stained sections of paraffin-embedded tissues fixed in a 10 per cent solution of formaldehyde, were as follows:

The incompletely expanded infantile parenchyma of the lung revealed vascular engorgement, focal hemorrhages, edema, and a slight pneumonitis. There was granular degeneration of the renal epithelium affecting particularly the convoluted tubules. An occasional small group of erythropoietic cells were in the sinusoids of the liver. Moderate fatty change had affected the central zones of the hepatic lobules. The splenic sinusoids contained histiocytes filled with coarse, brown, granular pigment. A microscopic, encapsulated cortical adenoma and focal hyperplasia of the zona reticularis of the suprarenal glands were present. Sections of the ovaries and Fallopian tubes were normal. The wall of the fundus uteri was formed by thin, stretched, irregular smooth muscle bundles lined by a poorly developed cytogenic membrane in which were dispersed a few fetal type endometrial glands. The lower portion of the uterus was lined by one or two layers of flattened pavement cells. A similar mucosa covered the septum and formed the lining of the cloaca, urogenital sinus, and rectum.

The colon, located within the septum, was lined with a partially autolyzed membrana propria. Its tunica muscularis was united to the septum by a thin fibrous layer. Sections of blocks taken on an oblique plane through the body wall between the blind end of the rectum and the anal dimple were composed of skeletal muscle bundles separated by a small amount of connective tissue, covered by panniculus adiposus and skin. Serial sections through this region should have been made to permit adequate study of the grossly described delicate cord connecting the blind end of the rectum to the anal dimple. It is thought this cord was an obliterated anal canal.

From an analysis of the developmental abnormalities encountered in the present report it would appear that during the sixth week of embryonic life complete division of the cloaca was arrested, resulting in its partial separation at its cranial

route was decided upon. Under general anesthesia, a normal female infant of 8½ pounds was delivered by classical section, after which a supracervical hysterectomy and bilateral salpingo-oophorectomy were done. Both broad ligaments were found to be quite free, and there was no evidence of extension of the neoplasm to the pelvic tissues.

The postoperative course was complicated by a low grade pneumonitis and a moderate secondary anemia, both of which responded to therapy. On the tenth day postoperative, the patient was transferred to the Radiotherapy Department for treatment of the cervical neoplasm.

From April 6 to May 9, 1938, the patient by deep x-ray received a total of 4,800 r. units, in daily treatments of 200 r. units each. A second course of 4,800 r. units was given from May 18 to June 16, 1938. Total x-ray therapy was 9,600 r. units.

On April 27, 1938, her condition seemed fair, and she had gained several pounds. Bloody vaginal staining persisted. The abdominal scar was firm and healed by primary union. The cervical stump was high in the vaginal vault and seemed to be adherent to the lower angle of the abdominal incision. The cervix was short, firm, and irregularly nodular throughout its entire extent. The finger could be inserted into the external os where it came in contact with friable tissue anteriorly and to the right. Moderate bleeding was caused by the examination.

On May 27, 1938: She had gained one pound in the past month and felt stronger than a month ago. She had had one episode of moderate vaginal bleeding. Abdominal scar was firm. The cervical stump was adherent to the lower angle of the abdominal scar. The external os was stenotic, flush with the vaginal vault, cartilaginous in feel and quite irregular. Fornices were free. There was slight bleeding on manipulating the cervix. Growth had apparently not yet involved the parametrial areas.

On June 17, 1938: There was no loss in weight. Occasionally there was slight vaginal bleeding, but no urinary or gastrointestinal symptoms. There was slight but definite early infiltration of both parametrial areas. Growth was still present in the cervix, which was flush with the vaginal vault.

On July 5, 1938, the patient was readmitted to the hospital for radium therapy. In the interval, she had gained five pounds and felt subjectively improved. At this time the hemoglobin was 40 per cent, and red blood count 2,600,000. Urine negative. Vaginal examination showed the cervix to be almost completely destroyed. In its place was a small stump with a superficial crater in its center. There was some infiltration of the parametria without fixation of same. Classified as early Grade B (Schmitz). She was given 6,500 mg. hr. of radium without reaction. Discharged July 11, 1938.

Patient again admitted to hospital July 21, 1938, with a diagnosis of a left sided pyelitis. Vaginal examination showed the cervix to be destroyed. There was an ulcerating crater at the vault. Bilateral parametrial tension was noted, more marked on left side. Excretory urography showed normal function of both kidneys and no ureteral obstruction. Hemoglobin was 62 per cent; red blood count, 3,150,000. Urine showed albumin, pus cells, and clumps. The pyelitis responded to simple therapy and patient was discharged Aug. 8, 1938.

Examination in the clinic on Nov. 28, 1938, showed her general condition to be excellent. There were no subjective symptoms. No vaginal bleeding. Vaginal examination showed epithelialization of the vault and practically no parametrial thickening.

Patient again admitted to the hospital Feb. 13, 1939, for additional radium therapy. Two weeks prior to admission, she began to have brownish vaginal staining, urinary frequency and burning. Vaginal examination showed nodular infiltration of anterior vaginal vault which was somewhat ulcerated again. Two radium bombs were applied directly to the indurated vault and the patient was given 2,600 mg. hr. of radium. At this time, her general condition was quite good. She had gained 20 pounds in ten months and felt quite well. Hemoglobin was 88 per cent; red blood count, 4,500,000. Urine was negative. A urogram done on Feb. 16, 1939, showed normal function of both kidneys, and a slight distention in the lower left ureter which was interpreted as probably being due to early ureteral involvement by the neoplastic process. Discharged March 2, 1939.

## FULL-TERM PREGNANCY COMPLICATING CARCINOMA OF THE CERVIX\*

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P. N., a 31-year-old Italian woman, made her first visit to the prenatal clinic Feb. 8, 1938. The family history and past medical history were completely negative. Menses began at 12 years of age, occurred every thirty days, and lasted seven or eight days. The bleeding has always been moderate in amount, and there has never been any dysmenorrhea, meno- or metrorrhagia. Last normal period July 15, 1937. Life was felt in October, 1937. Labor was expected on March 22, 1938. Marital history: Patient's husband had syphilitic cardiovascular disease for which he was being treated. She had had 6 children, all living and well; all delivered at home, weighing from 7 to 9½ pounds. All her labors had been easy. The oldest child was 13 years, the youngest 18 months. Wassermann test on the patient and on the children was reported negative. There were no stigmas of syphilis noted.

At this first visit to the clinic, physical examination revealed a short systolic blow at the apex, normal blood pressure and urine, normal pelvic measurements and an apparently normal seven and one-half months pregnancy. The cervix was soft and badly lacerated posteriorly, and the pelvic floor was markedly relaxed. Patient stated that she felt perfectly well during this pregnancy except for slight vaginal bleeding for one day each month. In October, 1937, she was admitted to another institution with an admission diagnosis of "probable tumor of the uterus." Correspondence with this hospital disclosed the fact that she was discharged after a three-day stay with a diagnosis of pregnancy. Examination at this hospital is reported as completely negative except for an irregular scar on the posterior lip of the cervix.

The patient made her second prenatal visit on March 8, 1938, at which time nothing unusual was noted. She returned again two weeks later, March 22, 1938, complaining of a slight show of blood. Examination showed the badly lacerated cervix extremely friable and it bled easily when touched. A small piece of tissue found on the examining finger was sent to the laboratory with a clinical diagnosis of possible malignancy of the cervix. The pathologic report came back March 25, 1938 as squamous cell carcinoma of the cervix.

The patient was admitted to the hospital on March 25, 1938. Examination at this time showed a somewhat poorly nourished, white woman of 31 years, with a full-term pregnancy. The vertex was dipping into the brim, and the fetal heart was heard in the left lower quadrant. Blood pressure was 120/70. Hemoglobin 57 per cent, red blood count 3,500,000; white blood count 8,500, polymorphonuclears 78 per cent. Urine negative. Heart normal except for a short systolic blow at apex. Lungs clear. Vaginal examination showed a relaxed pelvic floor and the posterior lip was described as lacerated, very firm, nodular, and irregular. The anterior lip was soft and smooth. The firmness involved the entire posterior lip as well as both lateral aspects of the cervix. In brief, the malignancy apparently involved over two-thirds of the entire cervix except for a small anterior portion. These areas were firm and nodular, not merely at the external os, but the firmness extended for about one inch in the long axis of the cervical body. The fornices were apparently free. Rough granular tissue found on the examining finger was again sent to the laboratory and the report came back once more "squamous cell carcinoma of the cervix."

One day after admission to the hospital, March 26, 1938, the patient began to have mild uterine contractions. Because of the degree of cervical involvement with its possible dangers of laceration, hemorrhage and sepsis, delivery by the abdominal

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## SIMULTANEOUS EXTRA- AND INTRAUTERINE PREGNANCY\*

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UP TO date approximately 300 cases of combined extra- and intrauterine pregnancies have been reported.<sup>1</sup> An extensive review was made by Neugebauer<sup>2</sup> who completed two studies, one in 1907 and the other in 1913, collecting a total of 244 cases. In 1926 Emil Novak<sup>3</sup> made a comprehensive study of the subject. He added 32 cases collected from the literature and reported two of his own, bringing the total at that time up to 278.

Of interest in addition to its comparative rarity, is the difficulty of accurate diagnosis. Of the 278 cases collected by Neugebauer<sup>2</sup> and Novak,<sup>3</sup> only 6.5 per cent were correctly diagnosed preoperatively.

One of us (B. L.) was called to see Mrs. F. C., a white woman, aged 39 years, who complained of vomiting, abdominal distention, and severe abdominal pain, radiating to her right shoulder. The patient was constipated. These symptoms first occurred two days previously. Her last regular menstrual flow had taken place two months ago. No bleeding had occurred since. She volunteered the information that she was pregnant for the tenth time. She has eight living children. On physical examination, the following were noted: Temperature 98.3° F., pulse 76, blood pressure 120/65. The patient appeared comfortable, color good, and skin dry. The abdomen was distended, and generalized, moderate tenderness was noted on palpation, particularly marked over the gall bladder and appendiceal regions. Vaginal examinations done when the patient was first seen and two days later, prior to a laparotomy, disclosed the following: The uterus was enlarged to the size of a two months' pregnancy, with definite tenderness over the fundus; however, similar tenderness could also be elicited over the entire abdomen except in the region of the adnexa. Putting the broad ligament on tension, by moving the cervix from side to side, produced no symptoms. Bulging in Douglas' pouch was not noted either by vagina or rectum.

Urinalysis was negative. The blood showed 87 per cent Hb. (Sahli), 12.5 gm. Hb.; 4,680,000 red blood cells and 8,400 white blood cells, with a normal differential count. Clearly the picture at this time was that of generalized peritoneal irritation, complicating a normal intrauterine pregnancy, with the gall bladder as the possible pathologic focus.

The lower bowel was cleansed by enema after two unsuccessful attempts. It is significant that the patient at this time fainted when she made an effort to leave her bed. However, her pain was considerably relieved and she had a restful night. The next day all the symptoms returned with greater intensity. She was then admitted to the hospital, four days after the onset of pain.

On admission, her temperature was 99° F., pulse 110, and blood pressure 120/65. The only change in the appearance of the patient, as noted several hours after admission, was a marked pallor. Sedimentation time was 31.5 mm. A flat plate of the abdomen showed a diffuse uniform haziness, not increased in depth over the lower abdomen. This was interpreted by the roentgenologist as being caused by the patient's marked obesity. Her blood count, however, showed a significant change: Hb. 50 per cent (Sahli), 7.3 gm. Hb.; 2,550,000 red blood cells, and 7,000 white blood cells, with a normal differential count. Both counts were done by the same technician.

On the basis of the second blood count and the change in the patient's appearance, a diagnosis of a ruptured ectopic pregnancy was made and immediate section

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The last admission to the hospital was on June 19, 1939, with the following history: The patient was well until April, 1939, when she began to have burning and pain in the rectal region and some rectal discharge. These symptoms were thought to be due to the previous radiation therapy. These symptoms improved for a while, but returned again in the month of May. During May, vaginal examination in the clinic showed nodular infiltration of the vaginal vault with some ulceration and sloughing. Both parametrial areas were contracted, indicating lateral involvement. The patient's general appearance was very poor and she had become completely inappetent. She had lost a good deal of weight and had become quite weak. One week before admission she developed severe lower abdominal cramps and diarrhea. On June 19, hemoglobin was 74 per cent; red blood count, 3,700,000. Urine was negative. An intravenous urogram done on June 23, 1939, showed a right-sided hydronephrosis not present in the previous pyelogram (February, 1939). This was interpreted as being due to pressure of the pelvic neoplasm on the right ureter. On June 26, 1939, the following note was made: "the patient looks markedly cachectic. Skin is dry, pale and loose, showing evidence of much recent weight loss. Vaginal examination shows a grayish discoloration of the very short cervical stump and anterior vaginal vault. These structures seem to be markedly infiltrated anteriorly, posteriorly and in both parametrial areas, so that the impression of a completely frozen pelvis is obtained. Moderate bleeding noted during examination."

Under conservative therapy of bed rest and sedation, the patient improved somewhat subjectively, the pain being less pronounced than on admission. She was discharged July 7, 1939, and institutional care in a chronic hospital was advised.

On Aug. 13, 1939, the patient was admitted to the Cancer service of the Kings County Hospital, and three days later she was transferred to St. Rose's Home, a home for incurables, in the Bronx. From this institution she was transferred to Welfare Island. For a long while, she was on the critical list, and according to the last inquiry a few days ago, she was said to be slightly improved. Her general condition was so poor, however, that death from either uremia or cachexia will undoubtedly occur very shortly.

#### SUMMARY

A case of full-term pregnancy associated with a fairly extensive cancerous involvement of the cervix is presented. The diagnosis of malignancy was first made four days before the patient went into labor. Delivery was accomplished by cesarean section followed by supracervical hysterectomy because of the degree of cervical involvement by the malignancy. As soon as the abdominal incision was healed, deep x-ray therapy was begun. This was given over a two-month period, so that the patient got 9,600 r. units. Shortly after this, 6,500 mg. hr. of radium were given. Several months later, additional radium (3,600 mg. hr.) was used. In spite of intensive radiotherapy, the malignant process, which in the first eight or nine months seemed to be under control, spread slowly but definitely. At the end of the first year, there was beginning involvement of the lower end of the left ureter, although the patient's general condition was still fair. By the end of fifteen months, there was a marked right hydronephrosis, and the patient was rapidly going downhill, with marked cachexia, abdominal cramps, and diarrhea. A frozen pelvis was present by this time. At the end of seventeen months the patient was on the critical list at Welfare Island, with the prospect that she would not live more than a few weeks.

right rectus was spastic. There was no vaginal bleeding; the uterus was softened, slightly enlarged. The cervix was soft and tender on motion. There was a definite fullness in the posterior and both lateral fornices. Urinalysis was negative. Blood count showed 4,100,000 red blood cells, hemoglobin 70 per cent, 19,000 white blood cells with 80 per cent polymorphonuclears. A diagnosis of ruptured ectopic pregnancy was made, and while waiting, the patient was given morphine, placed in Trendelenburg position, given applications of external heat and prepared for blood transfusion.

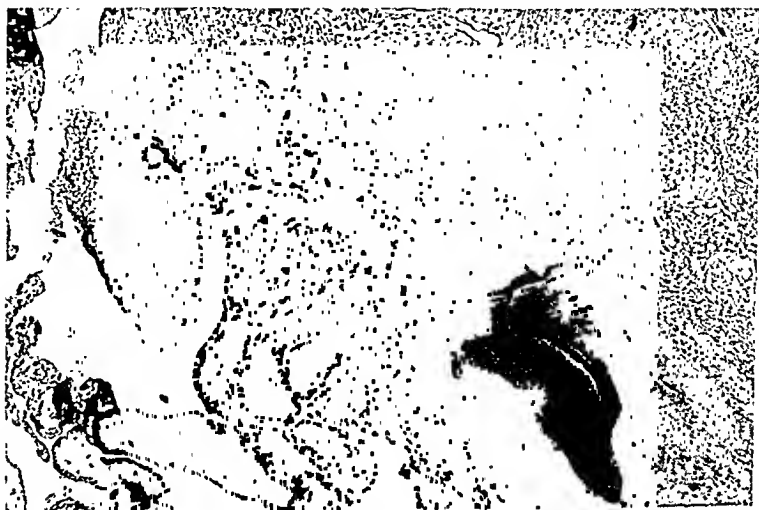


Fig. 1.—Photomicrograph ( $\times 80$ ) showing chorionic villi, hemorrhage, islands of decidua cells, and in the upper right hand corner, bordering islands of lutein cells.



Fig. 2.—Photomicrograph ( $\times 200$ ) showing higher power of the corpus luteum previously described, with detailed structure of lutein cells.

*Operation.*—Under nitrous oxide and oxygen anesthesia, a midline incision was made in the lower abdomen, and the peritoneal cavity was found to be filled with free and clotted blood. Both tubes and the left ovary were normal. The right ovary was found to be the seat of a recently ruptured cyst, containing a blood clot at its lateral pole. A right salpingo-oophorectomy was performed. The abdomen was closed without drainage and a blood transfusion of 500 c.c. of citrated blood was administered while the abdomen was being closed.

done. The abdominal cavity was filled with blood. The right tube was markedly enlarged, showing a rupture in the isthmal portion. The contiguous ovary was attached to the tube. The uterus was soft and was about the size of a two months' pregnancy. The left tube and ovary appeared normal. No corpus luteum was seen on the surface of the left ovary. A right salpingo-oophorectomy was done, a blood transfusion was given when the operation was completed and the patient was returned to her room. Within four days postoperatively she had a spontaneous abortion. She made an uneventful recovery.

*Pathologic Findings.*—"The specimen consisted of the right Fallopian tube and ovary. The ovary contained two corpora lutea, one measuring 2 cm. and the other 1 cm. The tube was greatly enlarged measuring 6 by 3 by 3 cm. At one region on its surface was a ragged hemorrhagic area probably representing the site of rupture and hemorrhage. Within the tube was a cystic area containing a tiny fetus, 1 cm. in length and to which was attached an umbilical cord. The wall of the contiguous tubal tissue was deeply hemorrhagic.

"In the hemorrhagic portions of the tube were many well-preserved chorionic villi. The cells of the larger of the two corpora lutea were large as is seen in the corpus luteum of pregnancy. A few cells of the smaller of the corpora lutea were also large, but the great bulk were of smaller dimensions.

"Microscopic examination of the tissue expelled from the vagina on 1-13-39, four days after the laparotomy, showed, in addition to much degenerated decidua and chorionic villi, many well-preserved chorionic villi."

Several months after discharge, the following noteworthy addition to the history was made by the patient, namely: that the abdominal pain started after she was kicked in the abdomen. However, had this fact been known it would only have added confusion to an already bizarre picture.

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### OVARIAN PREGNANCY\*

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MRS. L. E., 31 years of age, was admitted to the service of Drs. Schwartz and Schenck at the Jewish Hospital at 2 A.M. on Oct. 22, 1938, complaining of acute abdominal pain of eight hours' duration. During this time she had several fainting spells and also complained of marked thirst and weakness. She had three previous miscarriages and three normal deliveries, her last pregnancy terminating in a living normal child born ten months before admission. She had a twenty-eight day menstrual cycle, her last normal period having occurred on August 25. She stated that she skipped her September period and took quinine, after which she bled on October 2, one week overdue. On the afternoon prior to admission, after coitus, she was seized with severe abdominal pain, weakness and fainting spells. For the preceding two weeks she had noticed fullness of the breasts.

*Physical Examination.*—The patient was pale, restless, and had air hunger; pulse was 120, poor volume; blood pressure was 80/60, temperature 101.4° F., respirations 40. The abdomen was distended. There was marked tenderness and rebound tenderness over the entire abdomen but especially in the right lower quadrant. The

\*Presented at a meeting of the Brooklyn Gynecological Society, October 6, 1939.

## A SIX-YEAR CURE OF CANCER OF THE VULVA IN A TWENTY-TWO-YEAR-OLD PATIENT\*

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CARCINOMA of the vulva is characteristically a cancer of elderly women. In reporting this case, I wish to emphasize two salient and important features, namely, the age when first seen, 22 years, and second, that she is now alive and well, six years after her original admission.

In reviewing the literature on this subject, one is impressed by these two facts, of age incidence and high mortality, particularly in younger individuals.



Fig. 1.—Photograph (close-up) taken upon admission (July 12, 1933).

Taussig in one report gives the average age incidence of cancer of the vulva as 59 years, and another report by the same author, states that 60 per cent of the patients are over 60 years, and 30 per cent are over 70 years. Schrimmer and Wehr reported 118 cases, the youngest patient was 25 years.

I have been unable to find a report of a case of carcinoma of the vulva in one so young, who has remained alive and well after five years.

Patient, aged 22 years, was admitted to the Gynecological Ward of Hahnemann Hospital July 12, 1933, with a history of having a small pimple-like lesion on the right labia for several months, gradually increasing in size and ulcerating. This continued for about eight months, when immediate hospitalization was advised.

\*Presented at a meeting of the Obstetrical Society of Philadelphia, October 5, 1939.

*Postoperative Course.*—The patient's condition improved immediately after operation, and she made an uneventful recovery. She was discharged on Nov. 5, 1938, on the fourteenth day after operation.

*Pathologic Report.*—*Gross:* The specimen consisted of the right Fallopian tube measuring 8 by 0.4 cm. with the attached right ovary. The tube was normal and the fimbriated end patent. The ovary measured 4 by 3 by 2 cm. The external surface was yellow and gyrate and had a cystic hemorrhagic protrusion at one pole, measuring 1.5 cm. in diameter and filled with clotted blood. The cut surfaces of the ovary were gray streaked with brown and contained cystic areas up to 2 cm. in diameter filled with light brown material and surrounded by a thick yellow wavy rim.

*Microscopic.*—At one end of the specimen there was a broad lumen, containing old and more recently extravasated blood and strands of young fibroblasts. Scattered in the blood clots were well-formed chorionic villi with preserved Langhans and syncytial cells. Attached to some of the chorionic villi were sheets of decidual cells. Scattered within them were numerous syncytial giant cells. Part of the lumen was lined by a single row of flat cells resting on a normal band of hyalinized fibrous connective tissue and part of it lined by many rows of well-preserved, larger irregular lutein cells. Beyond this was a broad band of normal ovarian stroma with old and more recent corpora albicantes and small follicular cysts. In places syncytial giant cells were seen extruding into the corpus luteum that formed part of the wall of the lumen. A preparation from another corpus luteum that was seen grossly within the ovary showed an irregular lumen, containing old and more recently extravasated blood, and was lined by many rows of well-preserved lutein cells. These were irregular with abundant granular cytoplasm and large vesicular nuclei, and resembled in appearance cells noted in previous sections of corpus luteum. Bordering this was a band of ovarian stroma and old and more recent corpora albicantes and small and large follicular cysts. The microscopic sections of the right tube were normal and showed no trophoblastic elements.

*Diagnosis.*—Intrafollicular pregnancy of the right ovary with two corpora lutea of pregnancy.

We wish to thank Dr. David M. Grayzel for the careful pathologic studies.

3214 CLARENDON ROAD  
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Pinkert, M.: Treatment of Benign Uterine Hemorrhages in Women Over Forty With Special Consideration of Symptoms of Abolished Function, *Arch. f. Gynäk.* 168: 209, 1939.

The author discusses the nature of uterine hemorrhages and the irregularity so frequently found in women past forty. He discusses also the symptoms of abolished function of the uterus and ovaries, emphasizing the severity of the symptoms which arise from roentgen castration or radium therapy. He emphasizes the absence of such symptoms when such a diseased uterus is removed surgically with preservation of the ovaries. He believes that vaginal hysterectomy is superior to irradiation castration because of the ability to maintain and continue ovarian function. The same is true for abdominal hysterectomy for larger tumors. Irradiation entails less risk and definitely lowers mortality and morbidity. In spite of this and in spite of the fact that the author was one of the first to use roentgen treatment for fibroids and metropathia, he now resorts to this form of treatment only occasionally and only for the specially selected case. He has definitely arrived at the conclusion that surgery is the method of choice in spite of the somewhat higher morbidity and mortality.

RALPH A. REIS.

# Correspondence

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## Conservative Obstetrics

NOTE: We are pleased to publish the following letter as illustrative of the good results of the teaching of conservatism in obstetrics in our medical schools. The writer's conviction that a satisfactory outcome in adequately managed cases is to be expected, is worthy of attention and emulation.

*To the Editor:*

There has been considerable criticism in recent medical literature of the manner in which the modern physician conducts his obstetric cases. Putting it specifically, I quote from a recently published letter, in which the author accuses the modern physician of "altogether too much meddlesome midwifery."

Having graduated from a Class A medical school within the last four years I consider myself a modern physician. Although I am a general practitioner and have had no special training in obstetrics, other than that prompted by study, because this particular field of medicine appeals to me, I have had exceptionally good results. I attribute this to the application of the conservative methods taught me in medical school.

During my first two years in practice I attended 208 obstetric patients. About 75 per cent were cared for at home and the majority of these under very adverse circumstances with no professional assistance of any kind. I had no maternal deaths and not one patient had either a post-partum infection or hemorrhage. In 8 per cent of this series I encountered complications at delivery. These included a placenta previa in a primipara, 3 eclamptics and several pre-eclamptics, 4 breech presentations, a toxic jaundice of pregnancy, a retained placenta, necessitating manual removal seven hours after delivery, a syphilitic, a gravida iv with a severe mitral stenosis on the verge of decompensation, two pair of twins, one contracted pelvis that necessitated a cesarean section, 4 occiput posteriors that rotated and delivered spontaneously, and several cases in which labor was prolonged. These latter patients delivered without undue hardship because of repeated rest periods induced by the judicious use of morphine. Instruments were used in only two cases: one, the cardiac, whom I delivered with forceps under perineal block anesthesia as soon as she was completely dilated; the other, a patient that developed a maniacal psychosis soon after the onset of labor. Many of these patients had no prenatal care whatsoever.

In addition to the above obstetric cases, I operated upon two ectopic pregnancies and cared for several patients suffering from hemorrhage or infection or both following crudely induced abortions. There were no fatalities in this group.

My infant and fetal mortality combined was 3.8 per cent. This included 3 of 11 premature infants, 2 stillborn babies from eclamptic mothers, 1 stillborn syphilitic, 1 breech which had precipitated except the head and was dead when I arrived, and 1 apparently normal infant whose heart was beating after a normal and spontaneous birth, but who failed to breathe. Of the 8 premature infants that lived, one weighed only 3 pounds, another 3 pounds 6 ounces and, the remaining 6 less than 5 pounds at birth.

Nowadays with a large number of articles appearing in lay magazines exhorting the wonders of "twilight sleep" and "streamlined babies," it is becoming difficult to convince women that Nature's way is best. They forget to mention that sound-proofed rooms and special nurses are essential to handle patients rendered uncooperative by the effects of the drugs and also the fact that these procedures cause

Upon admission she had a large cauliflower mass of the vulva involving the labia on both sides, with apparent adenopathy in both inguinal areas (Fig. 1).

A complete vulvectomy, by electrothermic removal, was performed, followed immediately by radium application over each inguinal region. Two weeks later



Fig. 2.—Photomicrograph of section of tumor taken from margin, showing normal overlying skin with invading margin of tumor beneath. ( $\times 30$ .)



Fig. 3.—Photograph taken July, 1939. No evidence of recurrence.

a second series of radium exposures was given directly over the operative field. Deep x-ray therapy was instituted at once and continued regularly for about one year.

The total radium exposure amounted to 1,270 mg. hours, a relatively small dose and her x-ray therapy, given from Aug. 11, 1933, to Dec. 17, 1934, totaled 6,000 roentgen units through five portals of entry.



# Society Transactions

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## CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

*Eleventh Annual Meeting, Kansas City, Mo.*

*November 2, 3 and 4, 1939*

The following papers were presented:

**Presidential Address:** "James Henry Bennett, the Forgotten Man." Dr. Ralph A. Reis, Chicago, Ill.

**A Study of the Possible Significance of the Vaginal Smear as an Additional Factor in the Diagnosis of Incomplete Abortion.** Dr. Paul F. Fletcher, St. Louis, Mo. (For original article, see page 562.)

**The Management and Treatment of Habitual Abortion.** Dr. Ralph E. Campbell and Dr. Elmer L. Sevringhaus, Madison, Wis. (For original article, see page 573.)

**Intrauterine Death of the Fetus After the Twenty-eighth Week.** Drs. Henry Buxbaum and I. C. Udesky, Chicago, Ill. (For original article, see page 659.)

**Limitation of Human Reproduction.** Drs. H. C. Hesseltine, F. L. Adair, and M. W. Boynton, Chicago, Ill. (For original article, see page 549.)

**Spontaneous Pneumothorax of the Newborn Infant.** Dr. Edwin J. DeCosta, Chicago, Ill. (For original article, see page 578.)

**Post-partum Sterilization.** Drs. H. P. Hewitt and J. R. Whitley, Chattanooga, Tenn. (For original article, see page 649.)

**Post-partum Labial or Paravaginal Hematomas.** Dr. H. G. Hamilton, Kansas City, Mo. (For original article, see page 642.)

**Transverse Abdominal Incisions in Pelvic Surgery.** Dr. G. Wilson Hunter, Fargo, N. D. (For original article, see page 593.)

**Report of the Committee on Clinical Affairs: Chronic Cervicitis.** Dr. N. R. Kretschmer, Chairman, Ann Arbor, Mich. (For original article, see page 665.)

**Upon Certain Medical Philosophies.** Dr. Edward A. Schumann, Philadelphia, Pa.

**Granuloma Inguinale (Granuloma Venereum) of the Cervix.** Drs. R. E. Arnell, New Orleans, La., and J. S. Potekin, Chicago, Ill. (For original article, see page 626.)

**Further Studies on the Androgen Therapy of Gynecologic Disorders.** Dr. J. P. Greenhill, and S. C. Freed, Chicago, Ill. (For original article see page 636.)

**The Treatment of Bacteriemias With Sulfanilamide.** Dr. J. R. Reinberger, Memphis, Tenn. (For original article, see page 618.)

**Scarlet Fever in Obstetrics.** Dr. A. W. Diddle, Ray E. Trussell and Dr. E. D. Plass, Iowa City, Iowa. (For original article, see page 608.)

**The Induction of Labor With Small Doses of Powdered Ergot.** Drs. C. J. Ehrenberg, O. F. Robbins and John A. Haugen, Minneapolis, Minn. (For original article, see page 653.)

**Fat Metabolism in Pregnancy.** Dr. Otto Schwarz, St. Louis, Mo.

**The Newborn Infant.** Dr. Thomas J. Sims, Kansas City, Kan.

a sharp rise in the incidence of operative deliveries, maternal complications, and infant mortality. I am firmly convinced that a bit of humor along with encouragement when the going is tough is more beneficial and far less harmful than all the analgesic drugs now advocated for obstetric use.

In order to illustrate my point I will review the following case. One of the town's young matrons came storming into my office demanding an abortion. I finally convinced her to accept her condition, and she continued to come to me for prenatal care. As term approached she became very apprehensive and finally announced that she was going to have a cesarean section and have her tubes tied at the same time. I informed her that I was the one who determined the necessity of such procedures and that if she insisted upon it she would have to find another physician who would concede to her demands. Unfortunately she went three weeks past term in spite of several conservative attempts to start labor. She had a large baby in a right occipitoposterior position, and labor was prolonged. Twice during labor I gave her morphine which allowed her much needed periods of rest. No other sedatives or analgesics were used except nitrous oxide during the final stage of labor. The patient was very cooperative and never once made an outcry that could be heard in the hallway. The head rotated and the baby was born spontaneously. The patient was bright and cheerful the next day and stated that she did not think labor was half as bad as she had anticipated. They are now considering an addition to their family.

Although this series of cases is not large I believe the results were good, taking into consideration the number and type of complications, the lack of facilities for delivery, and the fact that a goodly number of these cases were primiparas who had had no prenatal care. By extreme patience and conservative handling I have encouraged many a mother on to a normal delivery where others would have interfered. I have been able to do this by retaining the confidence and cooperation of the patient. Patients readily sense any hesitancy on the part of the obstetrician, due to lack of confidence in himself, during prolonged labors or under trying circumstances. With loss of faith goes loss of courage on the part of both physician and patient. The former then feels forced to choose the most rapid and convenient method of getting things over with as soon as possible.

The day of elective radical procedures in obstetrics is rapidly fading and the pendulum is swinging back to conservative methods. Statistics bear this out. At the present time our state (Minnesota) boasts one of the lowest maternal death rates in the country. This is no doubt due to the fact that our medical school stresses conservatism in obstetrics, and for the men already in practice, the State Board of Health sponsors postgraduate lectures on obstetrics at various points throughout the state each year.

PAUL C. BENTON, M.D.

GIBBON, MINN.

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*To the Editor:*

The ensuing is a follow-up note on a case of "Sarcoma of the Uterus Complicating Pregnancy" which was reported in the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY*, 26: 457, 1933.

At this writing, more than nine years after the operation, the patient is alive and well. There are no metastases or recurrence. She has since been delivered of another child. In view of this history, it was thought that the original pathologic diagnosis may have been incorrect. The slides were then presented to the Tumor Conference of the Caledonian Hospital (Dr. W. Hala, Pathologist), and the original diagnosis reaffirmed. The slides were then taken by Dr. Hala to Dr. James Ewing, who confirmed the diagnosis. As far as I can find, this is the only published instance of its kind.

MAURICE G. DERBRUCKE, M.D.

January 18, 1940  
471 Park Avenue  
Brooklyn, N. Y.

# Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

## Selected Abstracts

### Endocrinology of Pregnancy

Klar, E.: Hormone Effect of the Ovum, *Klin. Wehnsehr.* 18: 600, 1939.

A substance was isolated from the ovum which produced abortion with great regularity in mice and rabbits. A similar effective substance was found in a series of cases in the urine of menstruating women, but this latter substance was not found with any degree of regularity. This substance which could not be completely isolated is believed to be a simple albumin. The author believes therefore that the dead ovum has a definite endocrine action.

RALPH A. REIS.

Hain, A. M.: Oestrogenic and Androgenic Substances in Pregnancy, *Edinburgh M. J.* 10: 678, 1938.

The estrogenic substances, "the female hormones," are responsible for heat or estrus in female animals. They are also present in the male. The androgenic substances, "the male hormones," are probably present in large amounts in the nonpregnant woman. They are responsible for certain male characteristics and are secreted by the ovary, testis, and the adrenal.

Marked differences in hormone concentration exist between individuals. It is advisable to make more frequent estimation of the hormone concentration than at monthly intervals during pregnancy, and during the last ten days daily estimation would be likely to give valuable information. It seems that the upward trend in hormone concentration which occurs in the last month of pregnancy is preceded by a relatively low level. There is no indication that very high values of estrin are necessarily associated with labor either in the combined or free form. By far the greater portion of the estrogenic substance excreted in pregnancy is found in the form of estriol. The androgens do not bear any quantitative relationship to the estrogens but show a tendency to share in the general hormone decrease at the ninth month and in the rise during the last month of gestation. There is less androgenic substance excreted by the pregnant than by the nonpregnant woman.

WM. C. HENSKE.

Mühlboeck, O.: Free and Combined Estrogens in the Blood During Pregnancy, *Lancet* 1: 634, 1939.

From 29 to 50 per cent of the estrogenic substances present in the blood of the pregnant woman are in the combined form. It is necessary to extract the blood after hydrolysis in order to obtain the total estrogenic hormone content. In many previous studies this has not been done. In 5 cases studied by the author, the total estrogenic hormone content varied from 150 international units per liter in a case of eclampsia to 2,000 international units in a normal pregnancy. A second normal pregnancy showed 750 I.U. per liter and a toxemic patient showed 900 I.U.

CARL P. HUBER.

## OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF OCTOBER 5, 1939

The following case reports and papers were presented:

**A Six-Year Cure of Cancer of the Vulva in a Twenty-Two-Year-Old Patient.** Dr. N. V. Ludwick. (For original article, see page 716.)

**Simultaneous Extra- and Intrauterine Pregnancy.** Drs. Benjamin Lefl and David R. Meranze. (For original article, see page 712.)

**Experiences With a Placental Blood Bank.** Dr. W. M. Heyl. (For original article, see page 679.)

**Intermenstrual Pain—A Surgical Condition.** Dr. E. F. McLaughlin. (For original article, see page 684.)

MEETING OF NOVEMBER 2, 1939

The following paper was presented:

**Roentgen Pelvimetry.** Dr. Herbert Thoms. (By invitation.)

## CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF OCTOBER 20, 1939

The following case reports and papers were presented:

**Two Cases of Brenner Tumor.** Dr. W. C. Danforth and Dr. H. J. Holloway (by invitation).

**Transperitoneal Approach in the Management of Inaccessible Vesicovaginal Fistulas.** Dr. W. C. Danforth. (For original article, see page 690.)

**Focal Infections in Pregnancy.** Drs. Tom D. Paul and Charles E. Galloway. (For original article, see page 694.)

**Premature Infant Mortality.** Drs. Robert M. Grier and Herbert O. Lussky. (For original article, see page 669.)

**Bipartite Uterus.** Drs. E. L. Benjamin and W. C. Danforth. (For original article, see page 704.)

## BROOKLYN GYNECOLOGICAL SOCIETY

MEETING OF OCTOBER 6, 1939

The following papers were presented:

**Full-Term Pregnancy Complicating Carcinoma of the Cervix.** Drs. Isidore Daichman and E. M. Wilder. (For original article, see page 709.)

**Ovarian Pregnancy.** Drs. Theodore H. Grundfast and Samuel B. Schenek. (For original article, see page 713.)

**Missed Labor.** Dr. William Pomerance. (For original article, see page 698.)

**Report of a Case of Tuberculous Endometritis.** Dr. George Kornfeld.

**Consideration on Rupture of the Uterus at Term.** Drs. G. Kornfeld and H. J. Greene.

fetal adrenals contain as much as, or more than, the placenta. Decomposition of tissue causes an increase in amount recovered from the placenta and a decrease in the liver. The general cholesterol metabolism is a more likely source of the estrogenic substances in pregnancy than the placenta.

J. T. WITHERSPOON.

Jones, Howard W., and Weil, Paul G.: *The Corpus Luteum Hormone in Early Pregnancy*, J. A. M. A. 111: 519, 1938.

In this case the corpus luteum of pregnancy was removed on the fifty-eighth day after the last menstrual period. Abortion did not take place. Following the operation, the daily urine content of pregnandiol, an excretion product of progesterone, was determined. For twelve days after the removal of the corpus luteum no pregnandiol was present in the urine. It then reappeared in increasing amounts. This seems to indicate that in the human being pregnancy can survive after the withdrawal of progesterone or that it can survive on amounts too minute to be determined by the method employed. Progesterone is probably produced by the placenta at about the end of the second month. Pregnanediol disappears from the urine within twenty-four to forty-eight hours after delivery, which would suggest that progesterone is produced in the placenta.

GROVER LIESE.

Gillman, J., and Smyth, G. S.: *The Hormonal Content of the Human Luteal Follicle of Pregnancy as Determined by Its Effect on the Perineum of the Baboon*, South African J. M. Sc. 4: 36, 1939.

Research in experimental physiology conducted by the authors has revealed some facts that are valuable as well as interesting. The hormonal content of human pregnancy corpus luteum was demonstrated by observing its effect upon the perineum of four mature baboons, all of which had menstrual or perineal cycles of known and equal duration (thirty-eight days). Comparison was made with the result of injection in the same animals of an oil emulsion of whole corpus luteum, and a commercial preparation of progesterone (proluton).

Human corpora lutea of early pregnancy are cystic and contain up to 1.5 c.c. of straw-colored fluid which possesses considerable potency. Those employed in this experiment were of a calculated maximum age of from sixty-three to seventy-seven days. Small measured amounts of the luteal fluid (1.0 c.c.; 0.5 c.c.; 0.25 c.c.) were injected into the baboons during the first or turgescient part of their menstrual cycle. The effects were compared with those obtained following injection of an emulsion in oil of whole corpus luteum, and progesterone substance (proluton). In general, both the luteal fluid and the preparation of progesterone had a similar qualitative effect, in that they caused perineal deturgescence when administered in a single dose early in the cycle. They differed, however, in the time factor of the physiologic response; progesterone being twice as rapid and not lasting long, while the luteal fluid was slower but had a more protracted action. Furthermore the luteal follicular substance definitely shortened the menstrual cycle, unlike single progesterone injections which lengthened the cycle. The series of perineal changes in the cycles experimentally induced by luteal fluid were quite similar to those observed in the second half of normal perineal (menstrual) cycles.

A number of conclusions were drawn from these and other experiments:

1. The fluid removed from the human corpus luteum of early pregnancy is not the same substance generally known as progesterone, having a different action and being more potent.

2. The luteal fluid is suspected to contain a hormone or hormones, hitherto unrecognized, elaborated by the corpus luteum. This is probably a potent gonadotropic factor for the existence of which direct evidence has been obtained from collateral experimental work on the rabbit.

3. Crude extracts (oil emulsion) of whole corpus luteum did not affect either the perineum or the length of the cycle.

Smith, G. Van S., Smith, O. W., and Pincus, G.: Total Urinary Estrogen, Estrone and Estriol During Menstrual Cycle and Pregnancy, *Am. J. Physiol.* 121: 98, 1938.

The writers comment on the "total" estrogenic potency of urine collected through a menstrual cycle and a pregnancy in a woman aged 27 years. The separation of theelin and theelol in the menstrual cycle revealed that (1) more theelin than theelol was present throughout, (2) more theelol was excreted during the luteal phase than during menstruation and excreted during the luteal phase than during menstruation and the period of follicle ripening, (3) a rise in theelin accompanied by the onset of menstruation, and (4) the theelin to theelol ratio was twice as high during the first two days of both catamenias followed as at any other time.

The separation of theelin and theelol through pregnancy revealed that (1) the only specimen which showed more activity in the theelin than in the theelol fraction was collected at the time of the second missed menstruation when the patient had been put to bed for flowing, (2) theelol was in the ascendancy for the rest of the pregnancy, its rate of increase being greater than that of theelin to the last month, (3) false labor twelve days before delivery was accompanied by a marked rise in both theelin and theelol, the ratio of the two remaining unchanged, and (4) in labor the rise in theelin was so great that the ratio of theelol to theelin was lower than it had been at any time since the second month. Comparison of colorimetric with bio-assay on the pregnancy urines from the fourth month on suggested the presence of some estrogen in addition to theelin and theelol and more active than either (estradiol).

J. P. GREENHILL.

Dingesmanse, E., Laqueur, E., and Mühlbock, O.: The Excretion of Estrogenic Hormone in the Urine of Pregnant Women, *Monatschr. f. Geburtsh. u. Gynäk.* 109: 37, 1939.

The authors found that the amount of estrogenic hormone which is excreted during pregnancy varies considerably. The extremes are 15,000 and 80,000 international units per liter of urine during the first half of pregnancy. It was found that about 97 to 98 per cent of the estrogenic hormone in the urine is the combined form. However, in most cases just before the onset of labor, part of these hormones is excreted in the uncombined or free form so that only about 80 or 90 per cent is combined estrin. During labor the amount of hormone excreted may decrease markedly.

The proportion of keton (estron) combination to non-keton (estriol) combination is 1:1 to 2:3 and is dependent upon the biologic effect during the last few months of pregnancy. During labor the proportions of the free fraction of estrin and the combined fraction change to 1:2 and 2:3, respectively. The proportion of keton to non-keton fraction in the urine of normal men and non-pregnant women is 1:1.

J. P. GREENHILL.

Parker, Frederic, Jr., and Tenney, Benjamin, Jr.: A Study of the Estrogenic Content of the Tissues in Pregnancy, *Endocrinology* 23: 492, 1938.

In five cases maternal and fetal organs have been extracted and assayed for their estrogenic substances and titrated against the placental content. In addition, the organs of 6 fetuses have been titrated against their placentas. The livers and adrenals of both mother and fetus have been studied because of their known involvement in the cholesterol metabolism. The effect of decomposition of the tissues on the amount of the estrogens extracted has been studied. The results have led them to believe that the source of the estrogens during pregnancy is in the general cholesterol metabolism. Although the placenta plays a prominent part, it is not the actual source. The maternal liver and/or the fetal liver contain more estrogenic substance in pregnancy than the placenta. The

uterus revealed no evidence of chorionic tissue. This is evidence that dissemination of tumor cells probably occurred at the time of curettage. The abrupt removal of practically the entire lesion by hysterectomy was followed by a lowering of the concentration of the gonadotropic hormone to the extent even of its complete disappearance from the blood stream ("negative phase"). This explains the first two negative biologic tests. The doubtful test which developed on the fourteenth day after curettement, and the positive tests which developed on the twenty-fifth and twenty-seventh days were probably due to the gonadotropic hormone elaborated by chorionepitheliomatous cells which entered the circulation and proliferated, having been disseminated at the time of curettage. This rapid increase in the blood concentration of hormone paralleled the equally speedy clinical course. It is possible that the concentration of gonadotropic principle in the blood might vary under the influence of factors yet unknown, for it has been shown that the hormonal concentration varies even in normal gestation. Support for this theory may be found in the fact that some portions of the tumor may be growing rapidly, while others are degenerating. Some of the metastases may become necrotic. Essentially, the quantity of gonadotropic hormones fluctuates and depends upon the vigor and the abundance of the chorionic elements by which it is elaborated.

In certain instances an apparent cure has been effected by the development of a dense proliferation of fibrous tissue about chorionepithelial foci sufficient to isolate them and prevent their hormonal secretion from entering the circulation. Should the syncytial elements outgrow the mesoblastic barrier, hormonal secretion may continue.

From an appreciation of the factors mentioned, the authors emphasize the fact that the occurrence of certain unexpected or paradoxical reactions in the biologic test for pregnancy does not detract from its usefulness and dependability. It continues to be of value in the diagnosis of chorionepithelioma, and especially in its control and prognosis.

ARNOLD GOLDBERGER.

Heiberg, Borge: Positive Friedman Reaction in a Case of Corpus Luteum Cyst, *Acta obst. et gynec. Scandinav.* 19: 176, 1939.

Felding and Neergaard demonstrated that a positive Friedman reaction may be found in patients having dermoid cysts of the ovary. As is evident from a case reported by Heiberg and from a few cases collected by him from literature, there is one more group of ovarian cysts, in the presence of which the urine of the patient may give a positive Friedman reaction, namely a corpus luteum cyst.

The case reported by Heiberg emphasizes three different observations that have been made before, namely: the similarity between the clinical features of corpus luteum cysts and extrauterine pregnancy, the occurrence of a positive Friedman reaction in patients with corpus luteum cysts, and occasionally changes in the pituitary in patients with corpus luteum cysts.

J. P. GREENHILL.

Schurger, S.: Can the Results of the Induction of Labor Be Improved by Estrin, *Zentralbl. f. Gynäk.* 63: 207, 1939.

Medical induction of labor is successful in only 50 per cent of cases. Schurger sought to increase this incidence by the addition of hormones. It is known that toward the end of pregnancy the amount of gonadotropic hormone gradually decreases, whereas the amount of estrin increases. Estrin increases the sensitivity of the uterus to pituitary hormone. A number of authors have reported that large amounts of estrin helped to stimulate labor pains in cases of uterine atony. Schurger used estrin in association with the Stein method of inducing labor. He gave castor oil and estrin in the early morning. Four hours later he administered thymophysin. Usually pains began within ten hours. By this combination he was able to increase the incidence of success in inducing labor to 80 per cent.

J. P. GREENHILL.

4. What is known as progesterone probably represents only a part of the hormonal complex.

No mention is made of the method by which these corpora lutea were obtained.

ARNOLD GOLDBERGER.

Hain, A. M., and Robertson, E. M.: Estimation of Luteal Activity and Early Diagnosis of Pregnancy, *Lancet* 1: 1324, 1939.

The possibility of using quantitative determinations of pregnandiol as a diagnostic test for pregnancy is illustrated by a case report. During routine investigation of a patient for habitual abortion, an excretion of 15 mg. pregnandiol per day on the twentieth to twenty-fourth days of the cycle led to the suspicion of pregnancy. This patient had excreted 114 mg. of pregnandiol from the twelfth to the twenty-fourth days of the cycle, while in the nonpregnant the range of excretion values is up to 60 mg. during this period of time. The Aschheim-Zondek test was negative on the twenty-eighth day of the cycle but became positive on the thirty-third day. A diagnosis of pregnancy was made one day before the menstrual period was missed.

CARL P. HUBER.

Lazarus-Barlow, P.: The Friedman Test in Hydatidiform Mole and Chorionepithelioma, *Brit. M. J.* 1: 71, 1937.

Four cases are reported in which the forty-eight-hour Friedman test proved valuable in diagnosis of hydatid mole and chorionepithelioma, following abortion in 3 cases and an abnormal pregnancy in one. The test reveals early the case of hydatid mole that passes on to chorionepithelioma.

The test is valuable in confirming complete removal of a mole and in disproving any pathologic significance of existing discharges. It serves to prove the absence of any secondary growths after removal of a chorionepithelioma.

F. L. ADAIR AND S. A. PEARL.

Keller, R., and Limpach, J.: Apparently Contradictory Results in the Biologic Test for Pregnancy Noted in a Case of Chorionepithelioma, *Gynec. et obst.* 37: 168, 1938.

The occurrence of several negative biologic tests for pregnancy in a patient upon whom the diagnosis of chorionepithelioma was made by histologic examination and proved by the subsequent clinical course forms the basis of this interesting report.

A curettage had been done followed six days later by a hysterectomy. The chronologic sequence and the results of the biologic tests were as follows: (1) Negative: eight days after curettage and two days after operation. Rabbit injected with 1/12 c.c. of urine. (2) Negative: thirteen days after curettage and seven days after operation. Rabbit injected with 60 c.c. of urine. (3) Doubtful reactions in several rabbits fourteen days after curettage, and eight days after operation. (4) Definite positive reaction with controls twenty-four days after curettage and eighteen days after operation.

The patient was discharged on her twenty-sixth postoperative day in good condition, with no x-ray evidence of pulmonary metastases, and the vagina clear. Within a month signs of "pleurisy" developed, and examination disclosed metastatic foci of chorionepithelioma. Her death occurred approximately fourteen weeks after her admission to the hospital.

Several possible explanations are offered for the apparent contradiction between the results of the biologic test and the histologic characteristics of the tissue obtained by curettage. The thorough curettage removed almost the entire lesion which from the beginning was probably a chorionepithelioma that had not spread beyond the limits of the uterine cavity. Except for the microscopic disclosure of a minute thrombus formed by a group of syncytial cells, the excised



Marian, and Watson cleared up this problem by showing that 99 per cent of the estrin which is excreted in the urine is physiologically inactive.

Friedrich treated two pregnant women who had pruritus vulvae with estrin, and the patients obtained prompt relief. No harm was observed. The patients at first received 20,000 international units hypodermically three times a week. After relief was obtained, only two injections a week were given.

J. P. GREENHILL.

**Fana, Camillo:** Experimental Research on the Endocrine Function of the Mammary Gland, *Folia gynaec.* 25: 419, 1938.

The author claims that in experimental animals the extract of mammary gland has shown an endocrine activity bringing on estrus and inducing a decided atrophy in the utero-ovarian region, but only in the presence of ovaries. He feels that the hypophysis is primarily stimulated and this, in turn, stimulates the ovary. In conclusion, the author states that the extract of the mammary gland gives good therapeutic results in any condition where an ischemia of the utero-ovarian region is desired, such as, menorrhagia, uterine fibromas, subinvolution of the post-partum uterus, etc.

MARIO A. CASTALLO.

**Hoffmann, F.:** The Effect of Estrin on the Histologic Structure of the Human Breast, *Zentralbl. f. Gynäk.* 63: 422, 1939.

For the first time, Hoffmann studied the effect of large doses of estrin on the histologic structure of the human breast. He obtained the tissue while performing plastic operations on the breasts. In a woman past the menopause, 50,000 estradiol benzoate units were given. The breast showed an increase in the milk ducts and a marked hyperemia. These changes are identical with those observed in castrated animals after the administration of estrin. In a second case, a woman in the reproductive age, a total of 250,000 units were given. The breast tissue was removed on the twenty-third day of the cycle and showed an increase in the milk ducts, an increase in the alveolar tissue, and extreme hyperemia and edema.

These results indicate that even with relatively small doses of estrin, morphologic changes may be brought about in the human breasts. They also show that, analogous to animal experiments, estrin affects the milk duct system, whereas the corpus luteum hormone in association with estrin controls the alveolar system. These results support the belief that until puberty the human breasts are only a milk duct organ and that only with the development of corpora lutea does the alveolar system begin to function.

Therapeutically the author advocates estrin to stop the secretion of milk, especially in cases of milk fistula after incisions for infection. In cases of breast abscess as well as in plastic operations on the breasts, estrin may help wound healing by its power of inducing hyperemia and stimulating growth of tissue.

J. P. GREENHILL.

**Preissenker:** Hormonally Induced Asymmetric Swelling of the Breasts Before Puberty, *Zentralbl. f. Gynäk.* 63: 451, 1939.

The author reports the case of a nine-year-old girl who received 35,000 international units of estrin because of gonorrheal vulvovaginitis. Shortly after this a painful lump developed in the right breast. With this there was excessive vomiting. Because of this combination of symptoms, corpus luteum hormone was administered to overcome the effects of the estrin. As a result of this therapy, all the disagreeable symptoms subsided. In three other girls treated with estrin before puberty, the author observed asymmetric breast swellings. Histologic studies were, of course, not made. On the other hand, in a 35-year-old woman, an adenoma was removed. This tumor developed a few weeks after 550,000 units of estrin had been given to overcome amenorrhea. Hence, estrin

**Cambon and Plasse: Estrin and Induction of Labor, Bull. Soc. d'obst. et de gynec.** 27: 466, 1938.

The authors report their results in attempting to induce labor with estrin in 21 cases. The patients were given 10,000 units daily for three days. If labor did not start, the patients were given quinine and pituitary extract. There were 8 primiparas and 13 multiparas. Labor was induced in only 2 of the 8 primiparas and only three times among the 13 multiparas. In 5 additional multiparas, quinine and pituitary extract succeeded in starting labor pains.

J. P. GREENHILL.

**Heckel, George P., and Allen, Willard M.: Maintenance of the Corpus Luteum and Inhibition of Parturition in the Rabbit by Injection of Estrogenic Hormone, Endocrinology** 24: 137, 1939.

Parturition in the rabbit is delayed by the continued injection of estrogenic hormone in the latter part of pregnancy. The ovaries must be present for this result to be obtained. In animals in which delivery has been postponed by this means, the corpora lutea are maintained and their continued activity is shown to be the cause for the delay in parturition.

Parturition is not delayed if injections of estrogen are not continued. Isolated injections in the latter part of pregnancy are followed by delivery of dead fetuses within four days. Under these circumstances the corpora lutea are not maintained. Cells of such corpora, by actual measurement, are smaller than those from corpora of normal pregnancy or from animals in which fetuses have been killed by estrogenic hormone but in which delivery has not occurred because of continuation of the injections. Doses of estrogenic hormone sufficient to delay parturition always cause death of the fetuses. A single injection on the twenty-seventh, twenty-eighth, or twenty-ninth day of pregnancy usually results in death of the fetuses within twenty-seven hours.

J. THORNWELL WITHERSPOON.

**Tsutsulopulos: Sex Hormone and Intestinal Activity With Special Reference to Atony of the Intestines During Pregnancy, Arch. f. Gynäk.** 168: 608, 1939.

Disturbances of intestinal function during pregnancy may be due to changes in the glands of internal secretion, alterations in the ion concentration, lack of vitamins, abnormal metabolic processes, constitutional and psychic changes, and also the activity of the sex hormones.

The author studied the effect of the sex hormones on the intestinal activity of rabbits. He found that pituitary extract stimulates the tonicity and peristalsis of both the large and small intestines. Estrin, likewise, augments the tonicity of the large intestines when given in large doses over a long period of time. Progesterin and prolactin when given over a long period of time diminish the tonicity of the large intestines and make this structure refractory to the effects of pituitary extract. Prolactin, however, has no effect in castrated rabbits. The effect of anterior pituitary hormone on the rabbit's intestines is uncertain.

J. P. GREENHILL.

**Friedrich: Hormone Treatment of Pruritus Vulvae During Pregnancy, Zentralbl. f. Gynäk.** 62: 1289, 1938.

Pruritus vulvae in the climacterium can readily be overcome by means of estrin. It occurred to Friedrich that the same kind of therapy could be employed successfully for pruritus of the vulva during pregnancy. Theoretically, it is illogical to give a pregnant woman estrin because during gestation there is a very large amount of estrin in the circulating blood and in the urine. It would appear particularly inadvisable to give estrin during pregnancy because large doses of estrin sensitize the pregnant uterus to contract. The investigations of Cohen,

additional doses need be given. The puerperium was not otherwise affected by the hormone, and there were no unpleasant aftereffects.

J. T. WITHERSPOON.

**Foss, G. L., and Phillips, P.: The Suppression of Lactation by Oral Oestrogen Therapy, Brit. M. J. 2: 887, 1938.**

Sixty-two cases are reported in which oral administration of estrogen (progynon) gave consistently satisfactory results in suppression of lactation. Ideally, treatment should be started soon after delivery, giving doses of 5,000 I.U. twice daily for one to four days. Rapid softening of hard, swollen, congested breasts with almost immediate relief of discomfort is reported. It is thought possible that estrone acts specifically on the mammary gland, in some way preventing the action of the lactogenic hormone of the anterior pituitary, or even by a direct antagonism to this lactogenic hormone.

F. L. ADAIR AND T. G. GREASY.

**Herold, L.: Morphologic Studies on Inhibiting Action of Estrogenic Hormone on Mammary Glands of Lactating Rats, Zentralbl. f. Gynäk. 62: 155, 1938.**

The administration of small doses of estrogen to lactating rats results in a partial inhibition of milk secretion. Large doses produce complete suppression of lactation, especially if the large dose is given immediately after delivery of the litter. This inhibiting action of estrogen is not limited to the time of treatment but persists. Microscopically in the mammary glands of the lactating animals treated with estrogen, one observes closed glandular alveoli that are free from milk and have an epithelium-like covering. There is also evidence of lack of secretory processes in the epithelial cells.

J. P. GREENHILL.

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## Books Received

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**FETAL AND NEONATAL DEATH.** By Edith L. Potter, M.D., and Fred L. Adair, M.D. University of Chicago Press, Chicago, Ill.

**OBSTETRICS AND GYNECOLOGY.** By the Departmental Staff of the University of Chicago and Other Contributors. Edited by Fred L. Adair, Mary Campau Ryerson, Professor and Chairman of the Department of Obstetrics and Gynecology, in the University of Chicago, etc. Volume I, 1,000 pages with 359 engravings and 14 plates. Volume II, 1,031 pages with 304 engravings and 10 plates. Lea & Febiger, Philadelphia, 1940.

**GRUNDLAGEN DER SCHWANGERSCHAFTEN-ERNAEHRUNG.** Von Dr. Med. G. Gaehtgens, Universitaets Frauenklinik zu Leipzig. 142 pages with 9 illustrations. Verlag von Theodor Steinkopff, Dresden, 1940.

**IL CICLO SESSUALE DELLE MADRI DELLE FAMIGLIE NUMEROSE.** A cura di Corrado Gini e Pia de Orchi. Comitato Italiano per lo studio dei Problemi della Popolazione. Roma, 1939.

**MANAGEMENT OF OBSTETRIC DIFFICULTIES.** By Paul Titus, obstetrician and gynecologist to the St. Margaret Memorial Hospital, Pittsburgh, etc. Second edition, 868 pages, with 368 illustrations and 5 color plates. The C. V. Mosby Company, St. Louis, 1940.

**SHOCK.** Blood Studies as a Guide to Therapy. By John Scudder, M.D. From the Surgical Pathology Laboratory of the College of Physicians and Surgeons, Columbia University, and the Department of Surgery, Presbyterian Hospital, New York. 315 pages, with 55 illustrations and five plates. J. B. Lippincott Company, Philadelphia, 1940.

may produce not only a hypertrophy of the uterine endometrium but also hypertrophy of the glands of the breast. The effects of excessive estrin stimulation are identical in the mature woman and in the prepubertal girl.

J. P. GREENHILL.

Fredrikson, Herbert: Endocrine Factors Involved in the Development and Function of the Mammary Glands of Female Rabbits, *Acta ost. et gynec. Scandinav.* 19: 1, 1939.

Experiments were carried out by Fredrikson on hypophysectomized and ovariectomized animals. In the absence of the pituitary, development of the structures of the mammary gland corresponding to that found in animals which were not hypophysectomized was obtained with follicular plus corpus luteum hormone. But little colostrum was secreted in these cases. The action exerted by the ovarian hormones on the mammary gland must be direct and not dependent upon the collaboration of the hypophyseal hormones.

The author's experiments show that, when the pituitary is removed, the mammary gland undergoes a development which is directly due to the animal's own corpora lutea.

The author's experiments also revealed that prolactin acts as a strong stimulant on the secretion of milk in castrated but not hypophysectomized animals in which the mammary glands have been developed by injections of follicular hormone plus corpus luteum hormone, and that the doses used had no gonadotropic, thyrotropic or adrenotropic activity.

In addition, prolactin was given to rabbits hypophysectomized toward the end of normal pregnancy or during lactation, the first injection being given four to forty days after the operation. In all the cases, milk was secreted within four days, even in mammary glands which had undergone pronounced involution, resulting from hypophysectomy during pregnancy or lactation. The secretion ceased a few days after the last injection of prolactin.

J. P. GREENHILL.

Adrian, J.: Therapeutic Value of Injections of Estrogen in Undesirable Lactal Production, *Gynec. et obst.* 37: 178, 1938.

Adrian resorted to treatment with estrogen, with the exclusion of all other therapeutic measures, in all cases in which an inhibition of the mammary secretion was justified, as in pulmonary tuberculosis, cardiac defects of the mother, stillbirth or early death of the infant. In some cases three injections of 20,000 international units are required; in other cases a single injection of this quantity is sufficient. This treatment proved successful in 57 per cent of 100 cases. In the other 43 per cent the results were insufficient, in that the secretion with expression of the breast persisted after the treatment. However, the result was nevertheless considerable in that the painful tension in the breasts, as well as the spontaneous secretion, ceased.

J. P. GREENHILL.

Kurzrok, Raphael, and O'Connell, Clinton Paul: The Inhibition of Lactation During the Puerperium by Testosterone Propionate, *Endocrinology* 23: 476, 1938.

Twenty-one cases of early lactation during the puerperium were treated with testosterone propionate, for the purpose of inhibiting lactation. Usually the inhibition of lactation by the generally used therapeutic measures, and especially in their absence, is associated with pain, tenderness, engorgement, and lumpiness of the breasts. Such breast symptoms require considerable nursing care and are very distressing to the patient. Testosterone propionate in doses of 25 mg. usually relieves such symptoms in about twenty-four hours without the addition of any other therapeutic measures. The hormone is injected twice within forty-eight hours, although if complete relief occurs after the second or third dose, no

- New England Obstetrical and Gynecological Society.** *President*, Thomas Almy. *Secretary*, R. J. Heffernan, 475 Commonwealth Avenue, Boston, Mass. May and December.
- Pacific Coast Obstetrical and Gynecological Society.** *President*, Alice F. Maxwell. *President-Elect*, John Vruwink. Meetings held in late fall or early winter, rotating in the larger cities of the Pacific Coast. Next meeting, San Francisco, Calif., Nov. 6 to 9, 1940.
- Washington Gynecological Society.** *President*, H. P. Ramsey. *Secretary*, James R. Costello, 900 17th Street, N. W., Washington, D. C. Fourth Saturday, October to May.
- New Orleans Obstetrical and Gynecological Society.** *President*, H. C. McGee. *Secretary*, H. W. Reddock, 1430 Tulane Avenue, New Orleans, La. Meetings held every other month.
- St. Louis Gynecological Society.** *President*, Percy H. Swahlen. *Secretary*, Joseph A. Hardy, Jr., 3720 Washington Blvd. Second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** *President*, T. Floyd Bell. *Secretary*, R. Glenn Craig, 490 Post Street, San Francisco, Calif. Regular meetings held second Friday in month, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** *President*, H. Reid Robinson, Galveston, Texas. *Secretary-Treasurer*, J. McIver, 714 Medical Arts Building, Dallas, Texas. Next meeting, Marlin, Texas, October, 1940.

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## Item

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### American Board of Obstetrics and Gynecology

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted at Atlantic City, N. J., from Friday, June 7, through Monday, June 10, 1940, prior to the opening of the annual meeting of the American Medical Association in New York City on Wednesday, June 12, 1940. Formal notice of the exact time and place of the examination will be forwarded to each candidate several weeks in advance of the examination dates. Group A candidates will be examined on June 7 and 8, and Group B candidates on June 9 and 10.

Candidates for *reevaluation* in Part II must make written application to the Secretary's Office *before April 15*.

The annual dinner of the Board will be held in New York City on Wednesday evening, June 12, 1940, at the Hotel McAlpin. Diplomates certified at the preceding days' examinations will be introduced personally, and there will be several speakers. All Diplomates of the Board, and others interested in the work of the Board, are cordially invited to attend this dinner. Tickets at \$3.50 each may be obtained from Dr. Joseph L. Baer, chairman, 104 S. Michigan Avenue, Chicago, Illinois, or at the registration desk during the examinations.

For further information and application blanks, address Dr. Paul Titus, *Secretary*, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

## ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES\*

(*Appears in January, April, July, October*)

- American Gynecological Society.** *President*, F. L. Adair. *Secretary*, Richard W. TeLinde, 11 East Chase Street, Baltimore, Md. Next meeting, June 17-19, 1940, at the Seignory Club, Quebec, Canada.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** *President*, James R. McCord. *Secretary*, James R. Bloss, 418 11th Street, Huntington, W. Va. Next meeting, September 19 to 21, 1940, Excelsior Springs, Mo.
- Central Association of Obstetricians and Gynecologists.** *President*, Jennings C. Litzenberg, Minneapolis, Minn. *Secretary-Treasurer*, W. F. Mengert, Iowa City, Iowa. Annual meeting, Indianapolis, Ind., October, 1940.
- South Atlantic Association of Obstetricians and Gynecologists.** *President*, M. P. Rucker, Richmond, Va. *Secretary*, Robert A. Ross, Durham, N. C. Next meeting, February 7 and 8, 1941, Jacksonville, Fla.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, Ludwig A. Emge. *Secretary*, Norman F. Miller, Ann Arbor, Mich. Next meeting, June 10 to 14, 1940, New York City.
- New York Obstetrical Society.** *President*, William S. Smith. *Secretary*, Henry T. Burns, 162 East 71st St., New York City. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** *President*, Thomas B. Lee. *Secretary*, John C. Hirst, 500 North 20th St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** *President*, Julius E. Lackner. *Secretary*, Edward Allen, 55 East Washington St., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** *President*, George H. Davis. *Secretary*, Bruce A. Harris, 175 Clinton St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Avenue.
- Baltimore Obstetrical and Gynecological Society.** *President*, J. J. Eastman. *Secretary*, Frank K. Morris, 11 East Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Building.
- Cincinnati Obstetrical Society.** *President*, E. W. Enz. *Secretary*, Edward Friedman, 19 West Seventh St., Cincinnati, O. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Esther C. Wallner. *Secretary*, Samuel S. Gordon, 520 Heyburn Building, Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Howard Stearns. *Secretary*, William M. Wilson, 545 Medical Arts Bldg., Portland, Ore. Last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** *President*, S. A. Chalfant. *Secretary*, Dr. Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, April, and June.
- Obstetrical Society of Boston.** *President*, Raymond S. Titus. *Secretary*, Judson A. Smith, 262 Beacon St., Boston, Mass. Third Tuesday, October to March, Harvard Club.

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\*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL.

Recently Zondek<sup>2</sup> surgically destroyed every ovum in the follicles of rabbits. He then injected "prolan" into these animals and brought about luteinization of the granulosa cells with a corresponding progestational change in the endometrium. Other laboratory experiments indicating the role of the corpus luteum in the production of progestational and gestational changes in the endometrium without fertilized ova date from the work of Leo Loeb<sup>3</sup> in 1908 when he produced deciduomas in guinea pigs by mechanical irritation of the endometria four to eight days after ovulation. The role of the ovaries in the production of deciduomas was proved by the failure of deciduomas to form if oophorectomy was done before the endometria were irritated. Ancell and Bouin,<sup>4</sup> in 1910, mated doe rabbits with vasectomized males and produced pseudo-pregnancy with deciduoma formation. Long and Evans<sup>5</sup> obtained the same result by simple mechanical stimulation of the cervix, whereas Shelesnoy<sup>6</sup> was successful in producing deciduomas by electrical stimulation of the cervix. Finally, Astwood,<sup>7</sup> has utilized these facts as a method of assay for progesterone. He stimulates the cervixes of rats electrically. Four days later, oophorectomy is done and progesterone supplied by injections of varying dosage. A comparison is then made between the degrees of decidual response in the test animals and the control animals which have been electrically stimulated but not oophorectomized.

From the above data there can be no doubt of the role of the corpus luteum hormone in the production of progestational and decidual changes in the endometrium and a fertilized ovum is not essential to real decidual change in laboratory animals.

In the routine study of endometria in our laboratories we have encountered many sections in which there seemed to be an excessive action of the corpus luteum hormone with a greater or lesser degree of decidua formation and no evidence could be found to indicate that the women were pregnant. In the first place, we wish to state that no one realizes more than we the difficulty in ruling out the possibility of pregnancy with absolute certainty. In many of our cases we believe pregnancy is unlikely. In a few we believe we have almost certainly excluded it. Beside the academic interest in this question there is a very practical one in the relation of deciduallike changes in the endometrium to ectopic pregnancy. We shall discuss this in the light of evidence which we shall present. We shall also consider the deciduallike changes in the endometrium in a nonpregnant virginal woman in the presence of a special type of ovarian tumor.

CASE 1.—(Gyn. Path. No. 46962 and 47009.) Patient was a 35-year-old woman who had had one spontaneous abortion five years before. The left tube was removed two years before. Menses were regular with twenty-eight-day intervals until her present illness. Her last regular period occurred April 26. On June 7 she began to bleed and bled continuously until the time of admission (twenty-three days). Since the onset of bleeding she had had abdominal pain. Pelvic examination showed a uterus of normal size and consistency and an adherent right adnexal mass about three times the size of an average ovary. Tubal pregnancy was suspected. A curettage and posterior colpotomy were done on July 4. No blood was obtained at colpotomy. The adherent mass was felt and thought to be inflammatory. An excessive amount of endometrium was obtained which microscopically showed an early decidual picture without chorionic villi (Fig. 1). Because of this and the presence of an adnexal mass, a tubal pregnancy was considered likely and a laparotomy was done. The left tube was found absent. The right-sided adnexal mass was formed by an adherent corpus luteum cyst and tube. Microscopically the cyst wall showed marked retrogressive changes (Fig. 1).

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## Original Communications

### DECIDUALIKE CHANGES IN THE ENDOMETRIUM WITHOUT PREGNANCY\*

RICHARD W. TE LINDE, M.D., BALTIMORE, MD., AND  
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*(From the Department of Gynecology, Johns Hopkins University and the Department of Obstetrics and Gynecology, University of Southern California)*

THE primary object of this paper is to draw attention to the possibility of a decidualike response of the endometrium to progesterone in the absence of pregnancy and to discuss the clinical importance of this in relation to functional uterine bleeding and the diagnosis of extra-uterine pregnancy. Is there any theoretical justification for the belief that decidua may occur without pregnancy? According to Robert Meyer's<sup>1</sup> theory of menstruation, a living ovum is essential to the life of the corpus luteum and it, in turn, is responsible for the progestational changes in the endometrium. Meyer's theory then assumes that the life of the corpus luteum of pregnancy is dependent upon a living fertilized ovum. Such is probably the case in a normally developing pregnancy since it has been shown by Hertig that the fertilized ovum puts out "prolan" at a very early date, which, experimentally, prolongs the luteal phase. There is, however, no evidence to show that the unfertilized ovum produces "prolan," and there is experimental work to indicate that the luteal phase of the cycle, which corresponds to the stage of pseudopregnancy in laboratory animals which do not ordinarily have a luteal phase, is not dependent upon the presence of a living ovum.

\*Presented at a meeting of the Chicago Gynecological Society, November 17, 1939.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."



though the endometrial picture shows changes beyond the usual premenstrual change, the stroma cells are less decidual in type than in the previous case.

CASE 3.—(U. M. H. 17660.) Patient was a 43-year-old married woman whose youngest child was 10 years of age. Six months before admission she had bled for three weeks. After seven weeks of amenorrhea she bled for three weeks and was bleeding at the time of admission. Pelvic examination was negative except for a minute fibroid in the wall of a retroverted uterus. A curettage showed very abundant endometrium which the operator thought was probably hyperplasia but which microscopically showed early decidua without chorionic villi.

In this case the endometrium has the appearance of early decidua. The picture corresponds to that which one would expect after seven weeks of amenorrhea, provided the amenorrhea were due to a prolonged progesterone effect. The only proof against pregnancy is the absence of chorionic elements in the tissue obtained by a thorough

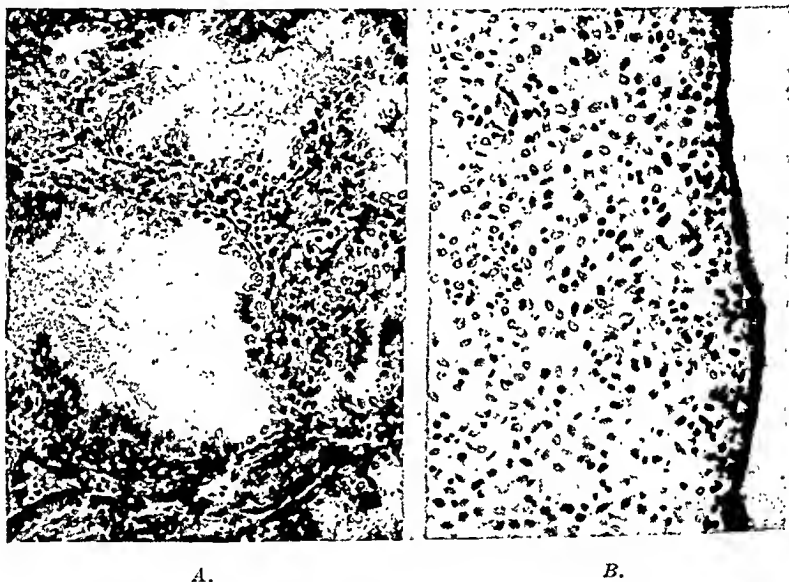


Fig. 2.—A, Secretory glands from spongiosa. B, Compacta.

curettage. This should be significant after seven weeks of amenorrhea for, had pregnancy existed and the patient been bleeding from incomplete abortion, the products of conception should have been sufficiently developed to have made it quite difficult to miss some trace of them in the curetted material.

CASE 4.—(Gyn. Path. No. 42307.) Patient was a 29-year-old woman who had been married nine years without becoming pregnant. Her complaint was sterility. She menstruated regularly at twenty-eight-day intervals. A biopsy of the endometrium was taken on the twenty-fourth day of the cycle. Sections showed an early decidua-like picture without chorionic villi (Fig. 3).

The absence of pregnancy for nine years before the biopsy and three years after makes it extremely unlikely that she was pregnant at the time the biopsy was taken. The glands were suggestive of the pregnancy type and the stroma cells of the compacta were decidedly

In this case approximately six weeks had elapsed since the last menstrual period before the onset of bleeding. The additional two weeks of progesterone influence had built up the endometrium into a decidualike picture. The wall of the corpus luteum cyst showed marked retrogression. Since she had been bleeding for twenty-seven days at the time of the curettage one must assume retrogression of the corpus luteum for at least that period of time. Tubal pregnancy was absolutely excluded by laparotomy. Intrauterine pregnancy with abortion remains a possibility but since she was still bleeding at the time of curettage, it is likely that there would have been some remnant of the products of conception left in the uterus had pregnancy been present. Since none was found in the scrapings obtained by thorough curettage, we believe the likelihood of pregnancy is slight.

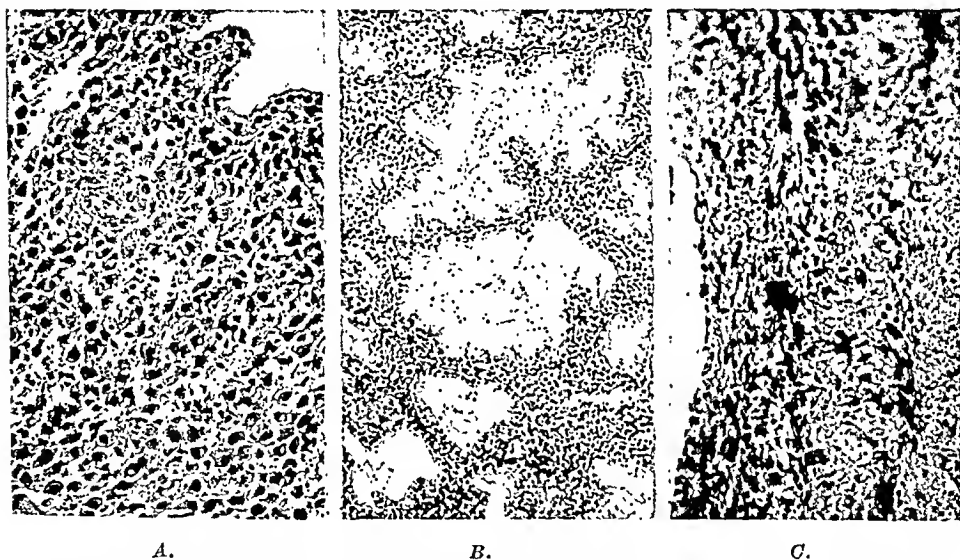


Fig. 1.—A, Compacta showing decidua cells. B, Spongiosa showing early pregnancy-like glands. C, Wall of corpus luteum cyst showing retrogressing lutein cells.

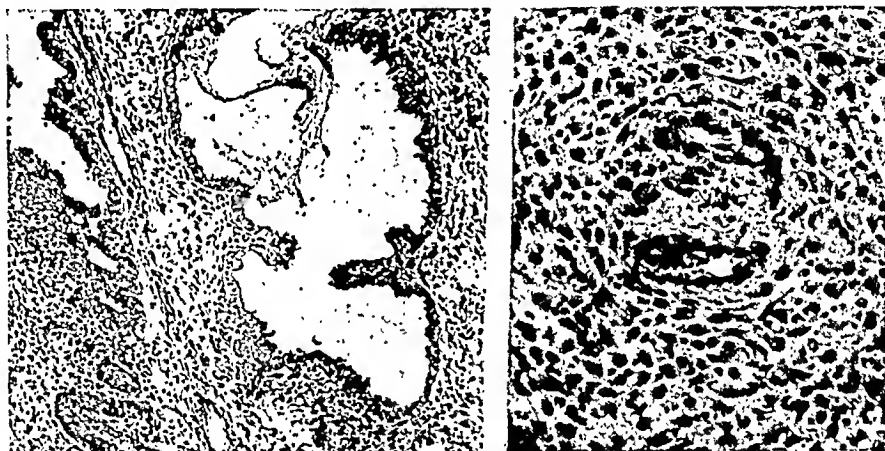
CASE 2.—(U. M. H. 14765.) Patient was a 22-year-old married woman who had been bleeding for two weeks. This bleeding was a continuation of her period which began on time, and the previous period had been normal. Since the onset of the bleeding, there had been some generalized lower abdominal pain but no acute pain. The pelvic examination was negative. A curettage was done and very abundant endometrium was obtained with no gross evidence of embryonic parts. Suspecting a tubal pregnancy, a posterior colpotomy was done and the tubes examined. They appeared normal. Friedman test for pregnancy done the next day was negative. The curettings showed early decidua without any chorionic villi (Fig. 2).

In this case we have again absolutely excluded tubal pregnancy and the absence of chorionic elements in the curettings is suggestive of the absence of an intrauterine pregnancy. This patient had missed no periods at the onset of bleeding and the progesterone had had less time to act upon the endometrium than in the previous case in which the bleeding was preceded by a period of six weeks of amenorrhea. Al-

however, that a cast without any villi is a rare exception when there is an intrauterine pregnancy.

CASE 6.—(Gyn. Path. No. B 969-39.) Patient was a 31-year-old woman who had had two previous pregnancies. She complained of profuse but regular menstruation. A curettage was done by a general surgeon. We were unable to learn the time of this operation in relation to her last menstrual period, but no periods were missed. The day following curettage the patient had a hemorrhage, and the surgeon did a hysterectomy. All of the curettings and the uterus were available for study. The endometrium showed decidua but no chorionic villi. No evidence of the embryo was found in either the curettings or the uterus (Fig. 7).

In this case we have only the gross and histologic evidence of no pregnancy in either the eurented endometrium or the entire uterus. There is still the possibility of complete loss of the fertilized ovum at the time of the bleeding following the eurentage.



A.

B.

Fig. 8.—A, Glandular changes are not particularly striking. B, Decidual changes in stroma cells are very marked, especially in the proximity of the blood vessels.

CASE 9.—(B 1055-39.) Patient was a 42-year-old married woman who had had but one pregnancy twenty-two years before. She complained of prolonged, profuse periods. A general surgeon operated upon her for supposed fibroids which were not found at operation. The tubes and ovaries were reported normal. A hysterectomy was done and the uterus sent to the laboratory for study. The endometrium showed no gross evidence of an embedded ovum and microscopically showed early decidua without chorionic villi (Fig. 8).

Unfortunately for the interpretation of the endometrium we were not able to learn the date of the last period prior to hysterectomy. Tubal pregnancy was ruled out by inspection of the tubes. The entire uterus was available for study. The endometrium had not been curetted, and no sign of an implanted ovum was found. We regard this as strong evidence against an intrauterine pregnancy, for a fertilized ovum of even eleven days is easily visible in the endometrium if looked for.

decidualike. This, we believe, represents simply an exaggerated premenstrual reaction on the twenty-fourth day of her cycle, possibly due to an excess of progesterone rather than a prolonged action.

CASE 5.—(Gyn. Path. No. 36897.) Patient was a 32-year-old married woman who had five children, ranging from 2 to 14 years of age. Her periods had been quite irregular for five years with considerable intermenstrual bleeding. She had bled three times during March for two days each, beginning on March 20, 25, and

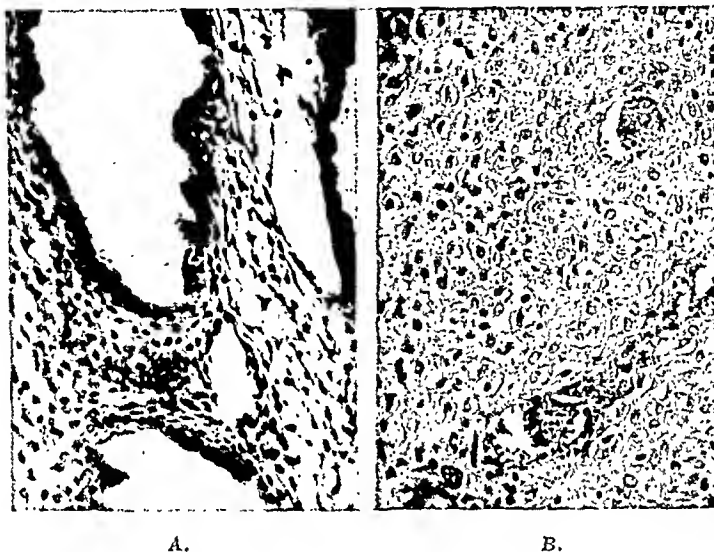


Fig. 3.—A, Glands. B, Decidualike change in stroma.

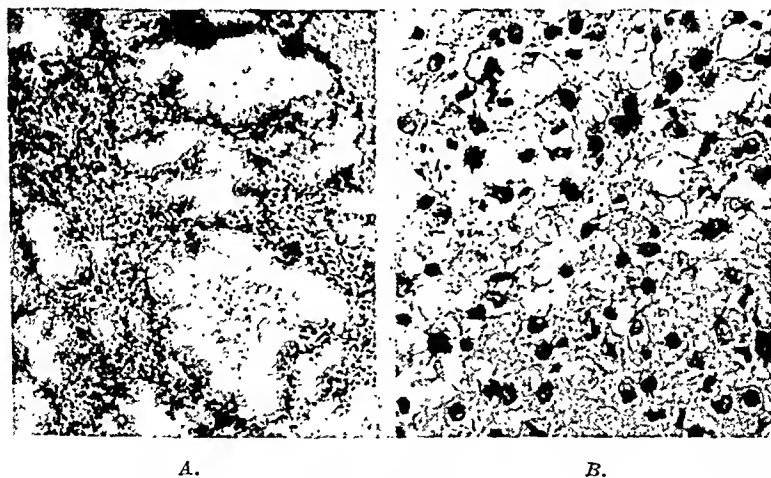


Fig. 4.—A, Secretory glands of early pregnancy type. B, Slight decidualike change in the stroma.

29. She was admitted to the clinic on April 23, complaining of right lower quadrant pain. The uterus was adherent, in retroposition and the adnexa were adherent. A curettage and laparotomy were done on April 25. The left tube was closed, forming a small hydrosalpinx. The right tube was bound down with adhesions but the fimbriated end was open. A left salpingectomy and uterine suspension were done. The curettings showed an early decidualike picture and no chorionic elements were found (Fig. 4).

were removed for "pus." In December, 1937, she bled three times for five, four, and seven days each. Since then she had bled two to three times each month and on admission she had been bleeding profusely for eleven days. Her breasts had been tender since December. On pelvic examination on June 21, 1938, the patient was found to be bleeding and a soft mass about 4 cm. in diameter was felt on the left. Otherwise the pelvic organs felt normal. A suction curettage was done on June 22, 1938. A large amount of thick edematous tissue was obtained. The microscopic examination showed a well-advanced decidua without chorionic villi (Fig. 10). Thinking that the patient must have been mistaken about the bilateral salpingectomy the operator felt that there was a pregnancy in the left tube. A laparotomy was done. Tubes were found to have been removed. The right ovary was normal in size and contained no corpus luteum. The left ovary was 5 cm. in diameter and contained a blood-filled cyst, which the operator thought was probably a hemorrhagic corpus luteum cyst. The uterus only was removed. There was no gross evidence of the products of pregnancy in the uterine cavity or microscopic evidence on examination of sections from several blocks. The endometrium showed a very well-developed decidua, with the characteristic pregnancy glands and large decidua cells. Whether this endometrial change is the result of too intensive or too prolonged progesterone

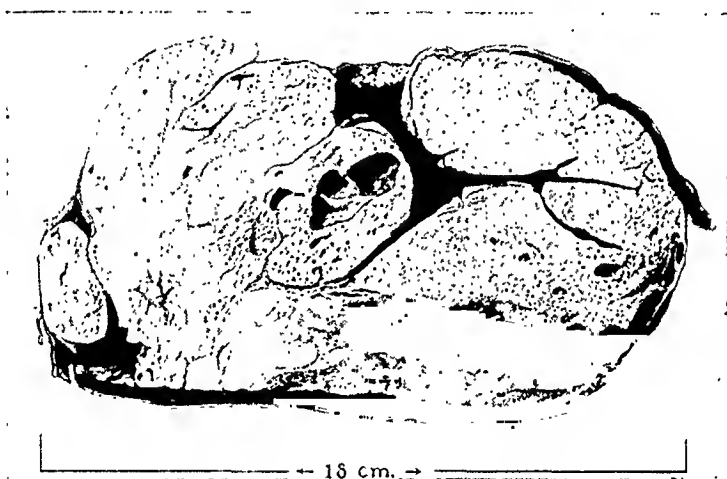


Fig. 11.—Gross specimen. The microscopic structure is seen in Fig. 12.

action is impossible to hypothecate on the basis of the history, but at any rate it seems that the absence of tubes plus the absence of any evidence of an ovum in the curettings or in the cavity of the removed uterus quite certainly exclude an intra-uterine pregnancy.

And finally, there is a case of a virginal woman in whom we believe an ovarian tumor was responsible for a deciduallike change in the endometrium.

CASE 12.—A 48-year-old unmarried woman was admitted as an emergency on July 3, 1938, because of difficulty in breathing. She gave a history of swelling of the abdomen of two weeks' duration with generalized abdominal pain and backache. For several months she had noted some suprapubic pain, especially when her bladder was full. Her menses were regular until three years before. She then began bleeding almost constantly, but for the past six months before admission there had been no periods or bleeding of any kind.

Abdominal and pelvic examination revealed a large ovarian tumor. The vaginal outlet unquestionably was virginal. Laparotomy revealed free straw-colored fluid in the abdomen. The pelvis was filled with a partially solid, partially

CASE 10.—(B 1070-39.) Patient was a 28-year-old woman who had been menstruating regularly at twenty-eight-day intervals for four to five days. Periods were always very painful. During the past four months there was a marked increase in profuseness of menstrual flow, and periods had lengthened to eight or ten days. Last period began on schedule, fourteen days before, and continued until a curettage was done because of continued flow. Curettings showed early decidualike picture without chorionic villi (Fig. 9).



Fig. 9.—Moderate gestational changes of both stroma cells and glands.

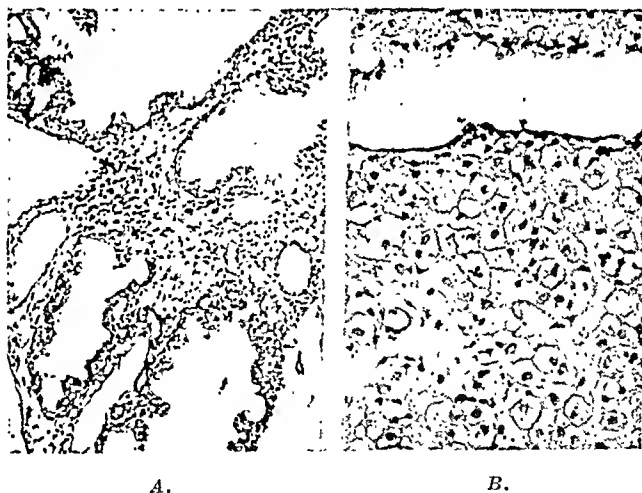


Fig. 10.—A, Gestational glands. B, Marked decidual reaction of stroma cells.

In this case we have only the absence of chorionic villi in curettings to disprove pregnancy, a fact which does not exclude it with certainty. However, no periods were missed and we are inclined to regard this endometrial picture as simply decidualike change, especially in the stroma cells, such as one frequently sees in the late exaggerated premenstrual phase.

CASE 11.—(A. C.) This case will be reported in a little more detail because we believe it illustrates our theme in a most conclusive manner. The patient, a 32-year-old woman, had had one child eight years before. Four years previously both tubes

of these glands were of the typical basalis type, showing no premenstrual or pregnancy changes, but a few showed a little serration, only slightly resembling progestational glands.

The tumor apparently belongs to one of the subdivisions of the granulosa cell group in which the tumor has taken on a lutein-like character. The microscopic picture corresponds to that of the tumor described by Lecéne<sup>9</sup> as "folliculome lipidique." We believe that the component cells represent maturation of the granulosa cells of the tumor, corresponding to that noted by Traut and Butterworth<sup>10</sup> in their experimentally produced granulosa cell tumors in mice. The history of almost continual bleeding for three years followed by six months of amenorrhea bears out this conception. Our theoretical assumption is that during the time of bleeding the tumor was of a typical granulosa cell nature, later maturing to the lutein type, producing progesterone and amenorrhea.

The literature of the past decade is filled with reports of granulosa cell tumors associated with endometrial hyperplasia. The belief that these tumors produce estrin is evident not only from the hyperplasia effect on the endometrium but also from the fact that implants of them have been shown to produce estrus in spayed laboratory animals. But when one searches the literature for authentic reports of the effect of these lutein-like tumors upon the endometrium, there is a paucity of exact observations. One sees mention of decidual changes in the endometrium associated with these tumors but accurate descriptions and photomicrographs are rare.

Benda and Kraus<sup>11</sup> report the case of a 38-year-old woman with a luteinized granulosa cell tumor who had amenorrhea for two years. On removal of the tumor she bled three days later, as is so frequently observed after removal of a corpus luteum. No curettage was done, however, and hence we have no knowledge of the histology of the endometrium. Dworzak<sup>12</sup> reported a case of a granulosa cell tumor in a 52-year-old woman who had menstruated regularly until two years prior to operation. Since that time there had been periods of amenorrhea of two to three months, alternating with bleeding spells of a day or two. Six days after removal of the tumor a membrane was passed per vaginam which grossly resembled a decidual cast. On section it showed decidual cells but the glands were not typical of pregnancy. The photomicrograph in the article shows an endometrial picture very similar to that of our case.

We believe that cases such as Dworzak's and ours are important, in that they strongly suggest progesterone secretion in this form of granulosa cell tumor and constitute one more link in our knowledge about tumors with hormonal activity. They also, in a general way, substantiate the general theme of this paper that decidual formation is possible without a fertilized ovum.

#### DISCUSSION

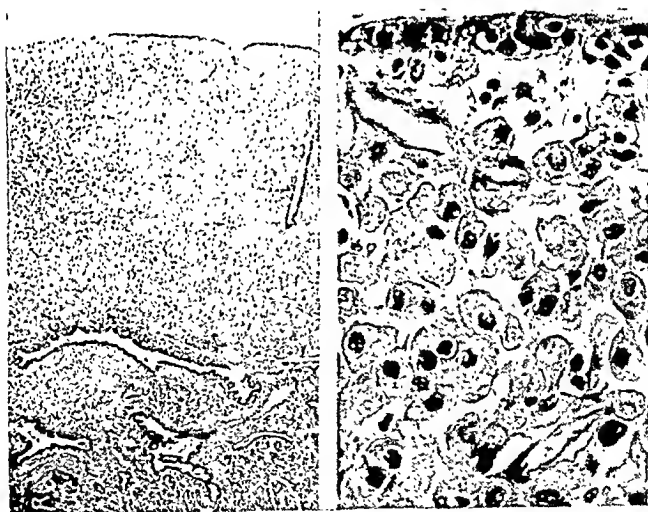
We have described several cases of decidual reaction in the endometrium in which pregnancy seems quite improbable and two cases in which it seems practically certainly ruled out. In one of these, there was a type of granulosa cell tumor which we believe was responsible for the decidual change in the stroma cells. In the other, the tubes had been previously removed and neither the curettings nor the removed uterus showed any ovum. With the exception of the one with

cystic ovarian tumor arising from the right ovary. The left ovary was very small and otherwise normal. The uterus was slightly enlarged due to several small fibroids. A hysterectomy and bilateral salpingo-oophorectomy were performed.

The tumor mass, which was composed of solid and cystic portions, was partially collapsed due to rupture of some of the cystic parts. It measured 19 cm. in diameter (Fig. 11). The unruptured cystic parts were filled with a clear brownish fluid. Projecting into the cystic cavities were irregular masses of friable yellowish tissue. The solid portion of the tumor varied between yellow and pink in



Fig. 12.—Section of granulosa tumor. The general architecture corresponds to that of Lecène's "folliculome lipidique."



A.

B.

Fig. 13.—A, Low power of endometrium, showing very heavy compacta layer. Glands are sparse and only a few show secretory change. B, High power of section taken near the surface showing very marked decidual-like changes of the stroma cells.

color. Microscopically, the general architecture of the tumor cells was similar to that of a granulosa cell tumor. Many of the cells were larger and contained more cytoplasm than the usual granulosa cells and suggested lutein cells in their appearance (Fig. 12). The endometrium was considerably thickened and composed of a solid mass of large clear cells, resembling well-developed decidual stroma cells (Fig. 13). A few slitlike glands are seen crossing the compacta here and there. There was no appreciable spongiosa, most of the glands lying in the basalis. Many



Such a picture was presented in some of our cases, some with and some without evidence of lutein cyst formation, and it raises the question of a similar prolonged activity of a noneystic corpus luteum. At any rate these cases suggest the possibility of a form of functional uterine bleeding associated with excessive luteal activity followed by a withdrawal of progesterone rather than abnormal estrogen effect as is generally believed to be the case in endometrial hyperplasia.

The relation of the above considerations to the interpretation of the endometrial picture associated with ectopic pregnancy is of considerable practical importance. Curettage is often of great value in the diagnosis of tubal pregnancy, but the microscopic picture must be interpreted correctly if it is to be of value. If subsequent observations bear out the contentions of this paper that decidua-like endometrium may exist without pregnancy, within or without the uterus, then the interpretation of the curettings becomes more difficult than we previously believed.

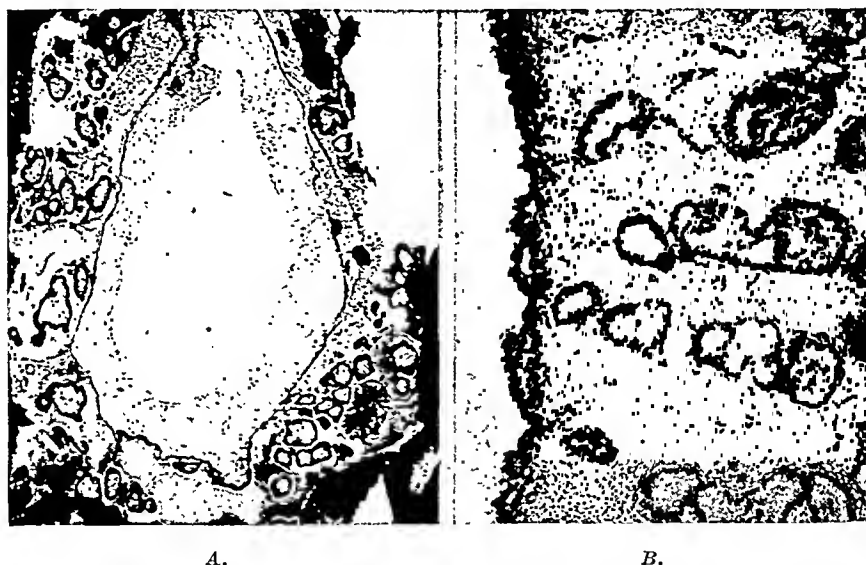


Fig. 14.—A, Early embryo found in tube. B, Endometrium from same case showing late interval secretory glands and absolutely no decidua-like change in the stroma.

We have always taught that the absence of chorionic villi in the decidual tissue obtained by thorough curettage is strong evidence against a uterine pregnancy. That it is not absolute evidence, however, is proved by the case which one of us reported in 1934.<sup>17</sup> Endometrium, obtained by a thorough curettage, showed a typical late premenstrual, or possibly early decidual pattern, but no chorionic elements were found. Without further coitus, the patient found herself pregnant after the curettage. Three months later a therapeutic abortion was done because of repeated, profuse hemorrhages. A live fetus was obtained which, according to Streeter, was of such age that it must have been present at the time the curettage was done. In spite of such rare cases, however, we still believe that curettings without any chorionic villi are rare in the presence of even very early pregnancy or uterine abortion.

the granulosa cell tumor, all of the patients in this series were married. This may be a significant fact in attempting to explain the presence of decidua. One must consider the possibility of the very early death of a fertilized ovum with absorption in the tube or expulsion from the uterus. Robert Meyer<sup>13</sup> apparently had this possibility in mind when, in considering similar cases, he wrote of "Schwangerschaft okkulta." However, in careful and complete sectioning of the uterus and tubes, he was unable to demonstrate any trace of an embryo. In the cases with very early decidua changes, there remains the possibility of the fertilized ovum being completely absorbed in the tube or completely expelled from the uterus. In our cases in which a previous bilateral salpingectomy had been done, the possibility of an intrauterine pregnancy is extremely remote. The decidua was well advanced in its development and, if one admits the remote possibility of pregnancy in the absence of tubes, the fertilized ovum would have to be developed to a corresponding degree. If such an embryo had been aborted and the patient's bleeding was dependent upon the abortion some trace of the fetal elements would almost certainly have been found in the curettings or the removed uterus.

Another theoretical explanation of the presence of decidua without pregnancy might lie in the wide variation in the amount of progesterone secreted. I shall not attempt to theorize on the underlying factors concerned in this variation. That there is a great variation in the amount of progesterone secreted in normal women is suggested by the variation in the amount of pregnanediol glucuronide eliminated in the urine of different women. Browne and Venning<sup>14</sup> concluded from their studies of the excretion of pregnanediol during the menstrual cycle that, "There apparently can exist all stages of activity of the corpus luteum and no doubt there may be considerable variation in the same person if sufficient cycles were followed." If the pregnanediol excretion is a true index of progesterone activity, one can readily understand an occasional excessive gestational or decidua change in the endometrium without pregnancy.

Several of the women in this series were bleeding, and it was for that reason that they were curetted. The question of the relation of this endometrial picture to functional bleeding is worthy of consideration. So much has been written about functional bleeding associated with endometrial hyperplasia that many have come to look upon the two conditions as almost synonymous. This, of course, is not true. In a series of bleeding cases studied in our laboratory Jones<sup>15</sup> found secretory endometrium in 17 per cent of the cases. In such cases we must assume some degree of corpus luteum activity. In considering the cases reported in our present series, the endometrial picture indicates either excessive or prolonged luteal action, and there is the possibility of prolonged bleeding resulting from degeneration of the corpus luteum with gradual withdrawal of progesterone from the endometrium which first had been built up to decidua by an excess of it. Halban<sup>16</sup> first called attention to the clinical picture of corpus luteum cysts resembling that of ectopic pregnancy with a period of amenorrhea followed by a period of bleeding.

removed at the time a hysterectomy was done. The embryo, according to Streeter, was approximately seventeen or eighteen days old (Fig. 14). The endometrium was intact, the glands showing a late interval or early premenstrual pattern, and the stromal cells showing not even the slightest decidual change (Fig. 14). Had a curettage been done one would not have had the slightest reason to suspect pregnancy.

The absence of decidua after the death of the tubal pregnancy is readily explained on physiologic grounds. The fetus dies; the corpus luteum degenerates; progesterone is withdrawn from the circulation; and the decidua is shed either in small fragments or as a cast. With the hormonal influence of the corpus luteum and the chorionic villi withdrawn, the endometrium may again resume regular cyclic changes. Two of our cases illustrate this.

In the first (Gyn. Path. No. 46690), the patient had been ill in bed six weeks before admission, with abdominal cramps. She had bled every two weeks since. There was a large fixed tender mass in the right side of the pelvis. A hysterectomy and right salpingo-oophorectomy were done. The section of the tube showed markedly hyalinized chorionic villi. The endometrium had an intact surface and the glands were of the postmenstrual type (Fig. 15).

In the second case (Gyn. Path. No. 44733), the patient had missed her September period and spotted through October with cramplike lower abdominal pain. She had no period in November, bled ten days in December, and failed to menstruate in January. She began what appeared to be a normal period on March 18 and was operated upon nine days later. The uterus and both tubes were removed. The endometrial surface was intact and the pattern of the postmenstrual type as one would expect on the ninth day of the menstrual cycle (Fig. 16).

Summarizing the possibilities of the endometrial picture in its relation to tubal pregnancy, one may say the following:

1. In tubal pregnancy there is frequently decidua without chorionic villi. The shorter the period of bleeding preceding the curettage, the more likely one is to encounter this picture.

2. In very early tubal pregnancy there may be no decidual change and the endometrium may not have advanced beyond the late interval or early premenstrual stage.

3. In an old tubal pregnancy with degenerated chorionic elements, the endometrial cycle may proceed normally after the decidua has been cast off.

4. The absence of chorionic elements in curettings showing decidua does not absolutely exclude intrauterine pregnancy or abortion, even though the curettage is apparently thoroughly done.

5. Excessive progestational effect with deciduallike changes in the endometrium may be found in cases in which pregnancy, intra- or extra-uterine, may be ruled out with reasonable certainty.

6. Since the clinical evidence and varied endometrial picture may leave the diagnosis of an ectopic pregnancy uncertain in some cases, we believe exploration through the posterior vaginal vault is a valuable procedure and should be resorted to rather than leave the diagnosis uncertain or perform a laparotomy on insufficient evidence.

It is now generally recognized that curettings may or may not show decidua-like changes in the presence of ectopic pregnancy and that the chances of obtaining decidua gradually lessen as the length of time of uterine bleeding increases. The combined statistics of Sampson, Geist and Matas, Moritz and Douglas, Boerner, Siddall<sup>18</sup> and Jarvis show an incidence of 72.1 per cent decidua in curettings in which the bleeding

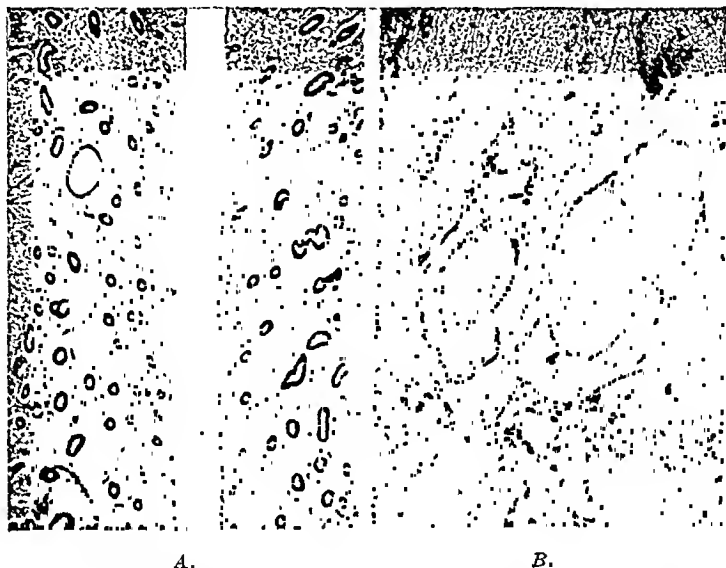


Fig. 15.—A, Endometrium of the postmenstrual type with surface epithelium intact. B, Hyalinized villi in the tube of the same case.

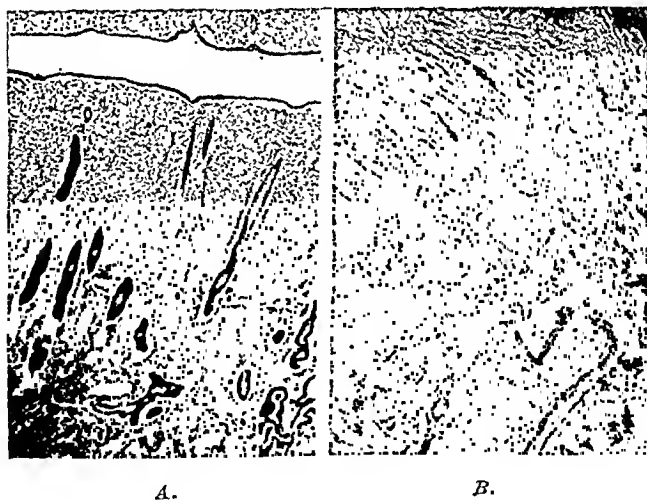


Fig. 16.—A, Endometrium glands of the postmenstrual type with surface epithelium intact. B, Old hyalinized chorionic villi found in the tube of the same case.

had existed for one week or less, and an incidence of 17.8 per cent in cases in which the bleeding had been present for more than twenty-nine days. Siddall and Jarvis found decidua in all of their cases in which the bleeding was of less than ten days' duration. That this is not universally true, however, is shown by our Case 45,976 in which a tube containing an unruptured, and apparently living, very early embryo was

the last few weeks. In the course of six months I became aware that I was having an unusually large number of short labors, which I could attribute only to the salt-poor diet. I then began a tabulation of the length of labors, the results of which I am reporting in this paper.

At first it was rather difficult to get patients to submit to a salt-poor diet, because it did not appeal to their appetite, and I could give them little in the way of a definite statement of its value. After a number of cases had accumulated, however, I felt confident to tell patients it would definitely shorten their labor, and few patients objected to their food not being well seasoned with that end in view. A little later patients began asking when they would have to quit eating salt, as they had heard of the treatment and results through some of their friends or acquaintances.

These 70 cases include 45 primiparas and 25 multiparas. For the sake of comparison I have also tabulated the duration of labor of 100 consecutive normal primiparas and 100 normal multiparas in the Missouri Methodist Hospital during the time the salt-poor diet was under observation. Included in the 70 were 13 cases of abnormal labors, and I have also included the similar abnormal cases occurring in the hospital during the same period wherein no special diet had been used. There were 15 in this group.

TABLE I. DURATION OF LABOR, NORMAL CASES

	PRIMIPARAS		MULTIPARAS	
	NO. OF CASES	DURATION OF LABOR	NO. OF CASES	DURATION OF LABOR
With salt	100	13.08 hr.	100	7.89 hr.
Without salt	34	6.58 hr.	23	4.30 hr.

Table I shows a summary of the results obtained in the normal cases, compared with the control series. In each of these groups the patients were regarded as normal at the time of labor, no fetal-pelvic disproportion, no abnormal presentation or position of fetus, and without marked evidence of toxemia or renal disease.

The duration of labors of the 34 primiparas who had been on a salt-poor diet ranged from 2.5 to 12 hours, with an average of 6.58 hours. The range of duration of labor for the 100 primiparas who had had no salt restriction was 3 to 48 hours, with an average of 13.08 hours.

Of the normal multiparas, the extremes of duration of labor of the 23 without salt were 0.5 hour to 10 hours, with average of 4.3 hours, whereas the 100 normal multiparas with no salt restriction ranged from 1 to 33 hours, with an average of 7.89 hours.

TABLE II. AGES OF PRIMIPARAS OVER 30 YEARS AND LENGTH OF LABOR

AGE	DURATION
31 years	7 hours
31 years	6 hours
32 years	3 hours
34 years	8 hours
35 years	11 hours
40 years	5 hours
Average	6.6 hours

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## SALT-POOR DIET AND ITS EFFECT ON LABOR

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THE relief of the pain and the lessening of the duration of labor are two of the greatest demands made on the obstetrician today, and they are far more important, in the minds of many laymen, than any amount of careful supervision of pregnancy and labor by a conscientious practitioner.

The demand for short and painless labors has led to the adoption of various procedures that are not all entirely without danger, such as routine version and extraction under anesthesia immediately after complete dilatation of the cervix; the use of pituitrin to hasten the latter part of labor; the excessive use of sedatives; the routine early use of forceps to terminate labor, etc. In the hands of experts any of these procedures can be used in most cases with good results, but in general use all of them present very definite dangers.

The search for the ideal method of relieving the suffering of child-birth has been in progress for many years, with a great number of preparations being brought forth to enjoy a short period of popularity, later to be replaced by something new. Still the ideal preparation has not been found.

In this paper it is not my purpose to advocate any new operative procedure to shorten labor, nor any new drug to lessen the pain of labor. I do, however, wish to report my results obtained in a series of 70 cases following the use of a procedure which does not employ any drug nor mechanical interference with labor, but which, I believe, does definitely shorten the duration of labor, and in a certain number of cases greatly lessens the severity of the labor pains. It is based on physiologic principles and consists simply of imposing upon the expectant mother a diet poor in salt during the last weeks of pregnancy.

Knowing the beneficial effect of a salt-free diet in toxemias of pregnancy, and the relative ease of labor of many patients who had been so treated for toxemia, I became interested in the possible benefit that might be derived by putting normal patients on a salt-poor diet during

TABLE V. TABULATION OF ABNORMAL CASES AND DURATION OF LABOR

PRIMIPARAS WITHOUT SALT		PRIMIPARAS WITH SALT	
TYPE	DURATION	TYPE	DURATION
Breech	9 hr.	Breech	11.0 hr.
L.O.T.	20 hr.	Breech	21.5 hr.
R.O.P., with hard } rigid cervix }	36 hr.	Breech	8.0 hr.
		Breech	42.0 hr.
R.O.T.	24 hr.	Breech	9.5 hr.
R.O.P.	20 hr.	Transverse	72.0 hr.
Breech	6 hr.	Breech	12.0 hr.
Breech	14 hr.	Breech	15.0 hr.
Brow	12 hr.	R.O.T.	32.0 hr.
R.O.P.	10 hr.	Average	24.7 hr.
L.O.T.	18 hr.		
L.O.T.	20 hr.		
Average	17.1 hr.		
MULTIPARAS WITHOUT SALT		MULTIPARAS WITH SALT	
TYPE	DURATION	TYPE	DURATION
Breech	6 hr.	Breech	6.0 hr.
L.O.T.	5 hr.	Transverse	12.0 hr.
Average	5.5 hr.	Transverse	6.5 hr.
		Breech	4.0 hr.
		Breech	14.0 hr.
		Transverse	12.0 hr.
		Average	9.1 hr.

the cervix is completely dilated. In most instances, this schedule allows just time enough to get the patient scrubbed and draped before she is ready to deliver.

While the chief advantage gained by the use of the salt-poor diet is the marked reduction of the duration of labor, it is our impression that these patients experience less severe labor pains than do other patients comparable in every other way. It has often been stated by these patients that labor really was not bad at all until just the last few pains. While the reduction of the pain of labor was not a constant factor in this series, it is of considerable importance.

Several of these patients had had mild toxemia of pregnancy but their symptoms had largely cleared up before the onset of labor.

There was no fetal or maternal mortality in this series, and no morbidity that in any way could be associated with the specific diet. The babies delivered in this series were of average weight. The lactating ability of the mothers did not seem to be affected in any way. The reduced salt diet was used during hot weather as well as during other seasons, with no noticeable effect.

Subsequent to the above observations, a search of the literature on the subject revealed an extreme paucity of material in English.

Bendlage, of Long Beach, California, reports a series of 5 cases, including both multiparas and primiparas, who had been on a salt-free diet for two months, whose labors lasted only from one to four hours. It was further stated that there was much less pain than normally experienced. The editor appended the parenthetical note: "This is a very interesting observation and worthy of the attention of anyone who is doing obstetric work, as it would be an easy and harmless plan to try."

The age range of the primiparas in the reported series was 18 to 40 years, averaging 25.5 years. Only two were less than 20, 28 were under 30, and 6 were between 30 and 40 inclusive. Of those above 30 years, the age and duration of labor are shown in Table II.

The age range of the 23 normal multiparas was 22 to 44 years. Eleven were below 30 years, 11 were 30 to 40 years, and 1 was 44 years of age.

The parity of the 23 multiparas varied from two to five. There were 15 para ii, 1 para iii, 5 para iv, and 2 para v.

Without reciting the figures in detail it may be stated that the age range of the 100 primiparas and 100 multiparas was essentially the same as the respective groups on salt-poor diet.

The abnormalities included in the series reported were of position or presentation of the fetus. While these groups are rather small, the results are still very interesting, and are summarized in Table III.

TABLE III. DURATION OF LABOR, ABNORMAL CASES

	ABNORMAL PRIMIPARAS		ABNORMAL MULTIPARAS	
	NUMBER CASES	DURATION	NUMBER CASES	DURATION
With salt	9	24.7 hr.	6	9.1 hr.
Without salt	11	17.1 hr.	2	5.5 hr.

It is difficult to explain the higher incidence of abnormal positions and presentations in the group with salt-poor diet. Certainly it is inconceivable that diet should in any way affect the presentation of the child. We frequently experience a number of similar complications in a short period of time, and then have a period comparatively free of such complications. Such was the case in this series, as about one-half of the abnormal cases occurred during a two-month period.

Another possible explanation is that the 200 normal cases were cared for by a large number of physicians, many of whom are not particularly interested in obstetric work, and it may be that there were some abnormalities in this group that were unrecognized, or of which no notation was made. This would have little bearing on the value of our observations, however, for grouping together normal and abnormal primiparas and multiparas, with and without salt, the results are still practically the same, as shown in Table IV.

TABLE IV. DURATION OF LABOR, ALL CASES

	ALL PRIMIPARAS		ALL MULTIPARAS	
	NO. OF CASES	DURATION OF LABOR	NO. OF CASES	DURATION OF LABOR
With salt	109	14.04 hr.	106	7.94 hr.
Without salt	45	9.15 hr.	25	4.39 hr.

The abnormalities observed, in the various groups, are tabulated as shown in Table V.

These labors are shortened chiefly in the first, or dilatation, stage, but there is also a marked reduction of expulsive stage. In fact, we have learned that it is advisable to take multiparas to the delivery room shortly before complete dilatation, and the primiparas just as soon as



The physiology involved has not been worked out in detail, and there yet remains a large amount of work to be done on the physiochemistry of the salt-poor diet, but we do have some working theories which seem well founded.

The most important physiologic effect appears to be a definite dehydration of the maternal tissues.

It is well known that there exists a physiologic decrease in the output of urine and a physiologic increase of water retention in the perfectly normal pregnant woman as she approaches term. This water retention is considered to be controlled by the posterior pituitary, and is a protective mechanism, providing a reservoir of water to act as a buffer in case of excessive hemorrhage at the time of labor, and to insure adequate fluids to be used in the manufacture of milk.

One of the large depots of this fluid reserve is the uterine musculature. The edema of the muscles impairs efficiency of uterine contractions, and edema of the cervix causes slower dilatation and increases the tendency toward lacerations. By decreasing the edema of the uterine muscles, we can obtain more nearly optimum conditions under which the muscles can work; thus the contractions are more effective, and the nonedematous cervix, being more elastic, responds with more rapid dilatation. Likewise the soft parts encountered at the outlet appear to be more elastic, and the expulsion of the child is much more rapid, and there are fewer perineal lacerations. This theory is borne out by the fact that patients with manifest edema in spite of the salt-poor diet derive little benefit so far as the reduction of the duration of labor.

That a salt-poor diet does cause a decrease of edema in most cases is without question. It is a common observation that a patient late in pregnancy may present pitting edema of the lower extremities, and after a week of salt-poor diet will show no edema and will have lost from one to several pounds of weight.

Water retention in the tissues is very closely associated with a chloride retention. Which is primary is open to question, as each seems to be necessary for the other. A salt-poor diet causes very little change in the blood chloride level, but when the intake is diminished, chlorides are withdrawn from the tissues into the blood stream, and thus some of the tissue fluids are released for excretion as urine.

Arthur, of France, has reported that giving the pregnant woman one pint of "dechlorinated milk" each morning, during the last few weeks of pregnancy, is very effective in removing the excess tissue chlorides, as this milk has a great affinity for chlorides. It is prepared by subjecting the milk to dialysis, with subsequent evaporation. When diluted to original volume, it contains about  $\frac{1}{8}$  the amount of NaCl found in the fresh milk. As yet I have had no experience with this method. It would seem, however, that an active dechlorinating agent that could be used so easily, would be most desirable.

Jahier called attention to a possible danger that may follow prolonged use of salt-free diet, namely clinical hypochloremia, and in support of his theory points out that these patients respond well to the administration of saline solution intravenously. He states that this manifestation is most likely in three types of patients: (a) where there has been much soft tissue damage during labor; (b) in

A search of the *Index Medicus*, the files of the library of the *A. M. A.*, and the files of the Surgeon General's Library has failed to reveal any other English article dealing with this subject.

The earliest reference available is the report of Hofstein and Petrequin of Strasbourg Clinic, France, in 1931. They reported a shortening of labor in patients who had been on salt-free diet for several weeks before labor. However, their treatment was rather complex, and it was difficult to determine whether the salt-free diet alone was responsible for the results.

In 1935, Karpati<sup>11</sup> observed a 34-year-old gravida iii, who had been treated for fifteen days in the clinic for nephropathy. She had hypertension, albuminuria, and marked edema. Her treatment was essentially a salt-free diet. Her labor started spontaneously and lasted only two and one-half hours. The woman experienced no pain until the expulsive contractions began about one-half hour before delivery. Karpati made note of the fact that there had been great improvement in the patient's condition before onset of labor, and he assumed a relationship between the salt-free diet and the very short and comparatively painless labor. This assumption was soon strengthened by reading the report of Hofstein and Petrequin mentioned above, though the two observations were entirely independent.

Reeb and Israel, of Strasbourg Clinic, followed up the work of Hofstein and Petrequin, and placed a number of patients on salt-free diet during the last several weeks of pregnancy, without any other form of treatment. In 1933 they published their experiences, stating definitely that the procedure did shorten the period of labor, dilatation being complete in all cases in from two to seven hours. They also noted a marked decrease in the severity of the pains experienced by these patients.

In 1935 Karpati<sup>9</sup> published his results in 50 cases in which he had used a salt-free diet. Thirty-three of these had a short and comparatively painless dilatation period. Of the 17 patients who did not show such marked results, all had had marked hypertension, albuminuria and edema, which had not improved with treatment prior to labor. Similar patients, whose symptoms had largely cleared up, all had short and easy labors.

There have been several other articles on the subject in the French, German, and Italian literatures, as indicated by my bibliography. The most comprehensive of these was published by Reeb. In this paper he reported a series of 100 patients whom he had placed on salt-poor diet during the latter weeks of pregnancy. Of these 56 were primiparas, and 44 were multiparas.

Of the 56 first labors he reported an average duration of six hours. The first stage of labor ranged from two hours. There were 3 more than six hours, 2 more than seven hours, and 3 more than eight hours (nine, twelve, and fifteen hours). These last 3 cases he regarded as failures. Two were cases of occiput posterior, and one had ineffectual spasmodic labor pains for a prolonged period.

Of the 44 multiparas in this series, the total duration of labor averaged three hours and twenty-five minutes. The extremes of the duration of the dilatation state were one to five hours.

It was observed by Reeb that of the 30 multiparas seen at the very beginning of labor, 15 had complete effacement of the cervix and engagement of the head at onset of labor. In 21 cases the anatomic preparation of the cervix was as complete as usually found in primiparas at the onset of labor.

In the series of 100 cases, there were only 14 instances of premature rupture of the membranes, as compared with 30 per cent premature rupture in the general run of cases.

Reeb declared that his patients who had been on a salt-poor diet experienced much less pain during labor than the general average of patients. This same observation has been made by several other authors, but is not nearly as constant as the shortening of labor.

Armand, of the School of Medicine of Haiti, reported beneficial results of salt-poor diet in shortening labor, especially in primiparas, and also marked reduction of the pain of labor. His results with multiparas were encouraging, but not so marked as most of the other authors have found.

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620 FRANCIS STREET

## ADVANCED ABDOMINAL PREGNANCY

WITH SPECIAL REFERENCE TO THE MANAGEMENT OF THE PLACENTA, WITH  
A REPORT OF THREE CASES AND REVIEW OF THE LITERATURE

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THE subject of ectopic pregnancy in general is ably discussed in all of the textbooks of obstetrics, but there is frequently meager space devoted to advanced abdominal pregnancy, and there is at present a wide diversity of opinion regarding the management of the placenta. It is this factor which usually determines the outcome of the case.

In 1933 Cornell and Lash published an excellent statistical review of abdominal pregnancy, their work being based upon 226 cases collected from the literature, together with 10 of their own. The publications cited date from 1919 to 1932. The maternal death rate in their series was 14.3 per cent, and they conclude that this rate could be lowered if no attempt was made to remove the placenta when it was evident that hemorrhage would be uncontrollable.

The present study is based upon the three cases herein presented, together with 66 additional cases reported in the English literature from 1933 to 1939. There were a few in which the data were insufficient for the present purpose and these were excluded.

Examination of the literature reveals that the condition, while not common, is not so rare as is generally supposed. Anyone doing obstetrics may at any time be confronted with the usually difficult diagnosis and the treatment of such a case.

A correct preoperative diagnosis is made in considerably less than half of the cases. From the study of Cornell and Lash and from the 69 cases included in this review, several rather constant factors stand

cases of prolonged persistent vomiting; and (c) in patients who have had specific therapy with the heavy metals. He cited specific cases illustrating each of these groups, but it was far from conclusive that there was any differentiation between his cases of so-called hypochloremia and shock, as we are accustomed to think of it, and for which intravenous fluids are the recognized treatment.

It may be well to take warning, however, that, with the use of the salt-poor diet and resultant dehydration, should the patient have unusual difficulties at delivery, profuse hemorrhage, etc., the body does not have the physiologic fluid reserve available for such emergencies, and we must be prepared to supply additional fluid promptly if indicated. It is also well to begin forcing fluids promptly after delivery to aid in the establishment of lactation.

The reduction of pain of labor by the use of a salt-poor diet is not nearly as constant as the shortening of labor, but it does occur often enough to be of great value and interest. However, it is not as easy to explain as the shortening of labor, and there is much experimental work yet to be done before we have the complete answer.

It has been pointed out that an increase of chlorides increases the excitability of the nerve centers, as illustrated by the fact that tabetics with absent knee jerks can be given large amounts of sodium chloride and the knee jerk will reappear in some cases. Further, some epileptic patients can be kept free of attacks by a salt-poor diet, and the attacks can be brought on at will by administration of rather large amounts of salt.

Van Noorden claims that a reduction of body chlorides causes a repartition of blood calcium, the total remaining unchanged, but colloidal calcium increases about 12 per cent at the expense of inorganic salts of calcium, and that this increase of colloidal calcium has a definite nerve sedative effect.

Schwarz also has investigated this question with similar results, though his increase of colloidal calcium ranged as high as 20 per cent, with the total remaining practically constant. He is inclined to believe, however, that the repartition is due to the decrease of the sodium ion rather than the chloride ion. Evidence that calcium exerts a sedative action on the nerve centers is to be found in the results of administration of calcium in cases of tetany.

The pain of labor may be regarded as a cerebral phenomenon provoked by peripheral stimuli—the uterine contractions. Thus we have a two-fold action: A reduction of the excitability of the nerve centers, and a definite nerve sedative effect, working together to lessen the severity of the pain experienced by the patient.

#### SUMMARY

The explanation of the action of the salt-poor diet may not be entirely correct in every respect, and certainly it is not regarded as being complete. Nevertheless the fact remains that a salt-poor diet during the last several weeks of pregnancy does definitely shorten the duration of labor, and in a considerable number of cases lessens the severity of the pain experienced by the patient. And there appears to be no contraindication to the use of the procedure.

It is my hope that this report may stimulate further investigation and wider use of this simple means of making labor less of an ordeal for parturient patients.

During the following week she felt well and there was no bleeding. On December 31, vaginal bleeding recurred, accompanied by abdominal "cramps," which she said were unlike her previous labor pains. Bleeding was profuse on this date, and spotting and intermittent abdominal cramping persisted until Jan. 3, 1939, at which time fetal movements ceased. At this time her doctor attempted to induce labor by castor oil and quinine. This was repeated several times, without success. There was also some cervical manipulation, evidently an attempt at dilatation and examination of the uterus, without success.

*Examination.*—The patient was an emaciated, anemic Mexican woman of about stated age. She appeared ill. General physical examination was negative except that having to do with the abdomen and pelvis. There was a tumor which filled the abdomen to within 3 inches of the xiphoid process. The fetal outlines were very distinctly palpable. The position was a breech, the head lying in the upper left quadrant. Fetal movements were not seen or felt, and the fetal heart tones were not heard.

Vaginal examination revealed the cervix small and firm, markedly anterior and pushed tightly against the symphysis. While the external os admitted the index finger, the internal os was tightly closed, and the uterine cavity could not be entered. There was a hard mass, impossible to displace upward, pushing down in the cul-de-sac beneath the posterior vaginal wall halfway to the introitus.

A firm mass could be felt above the symphysis about the size of a 2½ months' pregnancy, which seemed to be continuous with the cervix. It was not movable. This was thought to be the uterus. An attempt was made to insert a uterine sound through the cervix, but because of its position this was impossible. It was also impossible to insert a cannula or catheter into the uterus for the purpose of injecting lipiodol.

*Diagnosis of abdominal pregnancy was made.*

X-ray was requested, and the following report received: "Evidence of single pregnancy, breech presentation, apparently near term. Indistinct visualization of bones, disproportion of skull and angulation of spine suggest death of fetus. X-ray evidence is not conclusive for diagnosis of ectopic pregnancy without lipiodol injection of the uterus."

A small piece of tissue was passed from the vagina, upon which a pathologic diagnosis was made of decidual tissue, with necrosis and hemorrhage.

*Operation.*—Abdomen was opened in the midline below the umbilicus. The fetus was found lying in the abdominal cavity, mostly on the left side. The membranes were ruptured to a small extent and a knee was seen protruding through them. They were further ruptured and the macerated fetus extracted, which appeared to be that of an eight or a nine months' pregnancy. There were no gross abnormalities. The cord was separated at its placental attachment. No tie was necessary.

The uterus was enlarged to that of a three months' pregnancy. The placenta was found attached to the right side of the uterus posteriorly, to the right tube and the posterior surface of the right broad ligament, from which it dipped down into the cul-de-sac, and ascending, was attached to all the intestinal coils in the vicinity, including portions of the ascending and ptosed transverse colons. It was adherent to the omentum. There was beginning necrosis of the placenta and attached membranes. There had been no intraabdominal hemorrhage previous to the operation.

During the process of exploration of the placental attachments, one edge of the placenta was inadvertently separated, which was followed by rather profuse bleeding. A ring forcep was applied over this small area, and two figure-of-eight sutures placed and gently drawn down. Bleeding was entirely controlled.

No attempt was made to separate or remove the placenta, since its widespread attachment made this obviously impossible without uncontrollable hemorrhage. The membrane that was easily accessible was trimmed off and the abdomen closed in layers without drainage. A retention catheter was placed in the bladder. Post-operative condition was fair.

*Postoperative Course.*—The surgical convalescence was rapid and uncomplicated. Transfusion was given shortly after the patient was returned to her room, and

out as having particular value in the diagnosis of late abdominal pregnancy:

1. There is usually, if proper care is taken to obtain it, a history of signs and symptoms of early ectopic pregnancy, with probable tubal abortion.

2. The fetal movements are unusually noticeable to the mother, and are often constantly painful.

3. The fetus can be palpated with unusual ease.

4. There is frequently a degree of malaise and general disability which cannot be explained on the basis of the pregnancy itself.

5. The cervix, while it may occasionally show some softening, is usually described as being firm, resembling the nonpregnant cervix. There is seldom any effacement, and no softening or dilatation of the internal os. In the great majority of cases, special note is made of its position, which is high (anterior), and pushed against the symphysis. It is frequently to one side of the midline. Occasionally it is forced downward in the vaginal axis.

6. Frequently there is a history of what was thought to be beginning labor, which persisted for a time and ceased. The patient is frequently seen at this time. This episode is usually coincident with cessation of fetal movements.

7. The uterus, usually somewhat enlarged, is frequently palpable. Often this is mistaken for an ovarian cyst or a fibroid which is interfering with the onset of labor (which they would never do), or obstructing the birth passage (note in Case 3).

The x-ray is not very helpful, except in the occasional case when the diagnosis has already been sufficiently established by the history and physical findings to have preceded the x-ray examination by lipiodol injection of the cavity of the uterus.

The presence of all the above factors would be virtually diagnostic of abdominal pregnancy, and the presence of any one of them should make the attendant very conscious of its possibility. It will be noted that in the author's case reported below, all of them were present. They were all present in many of the cases reviewed, and two or more noted in all.

CASE 1.—F. H., aged 29 years, was admitted to the Obstetric Service of the Colorado General Hospital Jan. 12, 1939, with an outside diagnosis of pregnancy of eight or nine months' duration, with death of the fetus and placenta previa.

Patient had an uneventful pregnancy and delivery three years previously. There were no abortions. She dated her present pregnancy from the last regular menstrual period early in May, 1938. Nausea and vomiting followed shortly after, and persisted for one month. In June, there was a "menstrual period" which was prolonged, and which was associated with lower abdominal pain, more severe on the right side. Bleeding persisted for the first three weeks in June, then stopped, to recur July 4, at which time she had what she considered a normal menstrual period lasting three days. Following this the patient felt well until October 15, when fetal movements were first felt. She described these movements as very marked and painful. She stated that she could feel the outline of the baby's hand as it traveled across the abdomen, and could feel the fingers press against her. With the exception of these painful and marked movements, she continued without complications until December 25, at which time she passed numerous large clots from the vagina, without significant pain.

The abdomen was symmetrically enlarged. No fetal heart tones could be heard, or movements seen or felt. Numerous attempts were made to induce labor by means of castor oil, quinine, and pituitrin, all of which failed. Efforts to dilate the cervix for the purpose of introducing a Voorhees' bag failed because of the rigidity of the cervix, which was found high (anterior) against the symphysis, to the left of the midline. X-ray examination showed a breech presentation, with diagnosis of probable dead fetus, of about an eight months' pregnancy.

*Operation.*—The abdomen was opened, after it was found, under anesthesia, that the uterine cavity was small. The fetus, at or near term, was found inclosed in the membranes lying in the abdominal cavity. The placental attachment was to the uterus, tubes, and ovaries, all of which were incorporated in the mass. All except part of one ovary was easily removed, and the abdomen closed without drainage.

Postoperative condition was fair. The patient improved rapidly after a blood transfusion and intravenous glucose. Convalescence was uncomplicated, except for some trouble with distention for several days. She left the hospital on the fourteenth postoperative day in good condition.

CASE 3.—This case was obtained from the records of the Colorado General Hospital for 1932.

E. T., aged 33 years, first pregnancy, had been married for fourteen years. Menstrual history was normal. Appendectomy fourteen years previously. Last menstrual period Jan. 29, 1932 and was due on Nov. 5, 1932. She was admitted to the obstetric service with an outside diagnosis of missed labor and death of the fetus one week before. The detailed history of this pregnancy was not taken.

On admission, the patient was having what she thought were labor pains every fifteen to twenty minutes. During the remainder of the day of admission these pains continued, sometimes at intervals of five to seven minutes. They stopped during the night. On November 13, she was given castor oil and quinine followed by pituitrin in the attempt to induce labor, without success. On November 14, she received many injections of 3 minim doses of pituitrin, together with "cervical dilatation" by an interne. Contractions did not occur. A few crampy pains followed further injections of pituitrin.

On November 15, she was taken to the delivery room and under anesthesia a Voorhees' bag was inserted into the uterus. Following this, the patient had a chill and a rise in the pulse rate. Morphine was given some hours later for "pain in the abdomen," and the bag was removed. This was followed by considerable bleeding.

On November 16, she was taken to the operating room, with a preoperative diagnosis of intrauterine pregnancy, and what seemed to be a fibroid obstructing the cervix, "which was in reality a more or less normal uterus."

*Operation.*—On opening the abdomen, a large full-term fetus was found free in the abdominal cavity, except for many adhesions of the membranes and placenta to intestines and the peritoneum.

Adhesions were freed with considerable difficulty and some bleeding which was difficult to control. The fetus, placenta and membranes, and cord were removed, also a portion of the gangrenous omentum. The uterus was found to be about the size of a two months' pregnancy. The abdomen was closed with a Penrose drain inserted into the right iliac fossa.

The patient's course was steadily downward, and she died on the fourth postoperative day. At autopsy an additional portion of the placenta was found adjacent to the uterus.

#### DISCUSSION

In the review of abdominal pregnancy by Cornell and Lash, the maternal mortality rate was 14.3 per cent. In the 69 cases included in the present review, there were 13 deaths, a mortality rate of 18.8 per cent. If this difference cannot be correctly interpreted as representing

TABLE I

TREATMENT OF PLACENTA	RECOVERED		DIED	
	UNCOMPLICATED	COMPLICATED	CASES	RATE %
No attempt at removal:				
a. Abdomen closed without drainage or packing	8	4	0	0
b. Placenta marsupialized, or abdomen drained or pack used	1	4	5	50
Placenta partially removed, or unsuccessful attempts at removal:				
a. Abdomen closed without drainage or packing	1	1	0	36.3
b. Placenta marsupialized, or abdomen drained or packed	0	5	4	
Placenta easily removed in entirety:				
a. Abdomen closed without drainage or packing	21	0	1	4.8
b. Placental site packed, or abdomen drained	0	4	1	20
Placenta removed in entirety with difficulty:				
a. Abdomen closed without drainage or packing	0	2	1	22
b. Placental site packed or abdomen drained	2	3	1	

several intravenous injections of glucose were given during the next forty-eight hours. Her stay in the hospital was prolonged because of an extensive trophic ulcer which had begun to develop over the sacral region before her admission. This slowly healed, and she was discharged in good condition February 23.

During the time she was in the hospital, the placental mass gradually decreased in size, although at the time of discharge it was still palpable 3 fingers below the umbilicus. The abdomen was not unduly tender. There were no bladder or intestinal symptoms. She was instructed to return in three months for examination.

The patient was examined June 17. She appeared to be, and stated that she was, in excellent general health. Menstruation had occurred for the first time May 30, and was entirely normal.

The operative scar was well healed. There was marked diastasis of the recti muscles. There was no complaint of pain or tenderness on deep palpation of the abdomen.

Examination below was essentially negative. The cervix was in normal position, the vaginal vault was soft and the cervix freely movable. Bimanual examination revealed the uterine corpus of normal size, in good position and freely movable. There was a flattened mass, about 2 inches long, back of, and extending slightly to the right of the uterus. Uterus and mass could not be completely separated by the examining fingers, but both were freely movable. Both ovaries were palpable and normal. There was no palpable tubal pathology.

Tubal insufflation was done. The initial pressure was raised to 170 mm. of mercury before the gas began to pass, after which it passed readily through both tubes at a pressure of between 70 and 90 mm. of mercury.

CASE 2.—This private case, at which the writer assisted, is included by courtesy of Drs. M. A. Spangleberger and G. Heusinkveld, of Denver.

M. B., aged 28 years, had had one normal pregnancy five years previously, followed by 2 spontaneous abortions at about six weeks. The puerperium and postabortal courses were normal. The last menstrual period in the present pregnancy was April 20, 1928. She was due Jan. 27, 1929. The details of the course of the present pregnancy are not obtainable. She was admitted to the hospital Feb. 14, 1929, with a diagnosis of missed labor and intrauterine death of the fetus one week before.



centage of uncomplicated recoveries; viz., 21, or 91 per cent, with one death and no uncomplicated recoveries. But in this group in which drainage was used, there is one death and four complicated recoveries, and *no* uncomplicated ones. Since in this group it is noted that the placentas were easily removed, it would appear that the employment of drainage in these cases was entirely a matter of preference.

The high mortality rate, 36 per cent, and the high percentage of complicated recoveries, 54.5 per cent, in the group in which the placenta was partially removed, or in which unsuccessful attempts were made to remove it, attest to the unwisdom of such attempts in those cases in which the character of the placental attachments should clearly forbid them. The very unfavorable results in this group in which packing or drainage was used are about equal to those in which marsupialization of the undisturbed placenta was employed. Although in this group packing or drainage may have been a matter of necessity, because of hemorrhage, etc., and not of choice, the factor of drainage itself cannot escape a strong suspicion of guilt in the unfavorable results.

It appeared that in numerous instances, the indication for drainage was necrosis of the placenta and membranes. It should be recognized that necrosis and liquefaction of the placenta is the necessary first step to its absorption. Such a field is a most fertile one for the implantation and growth of infection. Leaving the abdomen open in the presence of such a field permits the entrance of infective organisms and nullifies the aseptic care under which the operation itself was done. In the absence of infection, the peritoneum and omentum appear to be admirably able to take care of even a complete placenta and membranes.

#### CONCLUSIONS

1. Factors in the diagnosis of advanced abdominal pregnancy have been enumerated above.

2. If the placenta is so situated that it can be *easily* removed, without damage to vital structures or without undue consummation of time, and when the circulation to it can be easily and completely controlled by ligature, this should be done, and the abdomen closed without drainage.

3. If observation and *gentle* exploration show that this is not possible or probable, no attempt should be made to remove the placenta, and again the abdomen should be closed without drainage. Marsupialization of the placenta, or drainage of the abdomen with the placenta left in appears to be the worst treatment of all.

4. Necrosis of the placenta and membranes is a physiologic process, and should not of itself be an indication for drainage.

5. Mortality and morbidity rates for this condition appear to be much higher than they need be. The factors which should lower these rates are (1) earlier recognition by having the possibility in mind in cases showing one or more of the diagnostic points noted above, which would prevent loss of time before operation, and dangerous and futile attempts to "induce labor," and (2) better surgical judgment at the time of operation, chiefly in regard to management of the placenta.

an increase in the mortality from surgery in abdominal pregnancy, it can safely be said that there has been no apparent improvement in the results in this condition in the past twenty years. The following analysis is an attempt to determine some of the factors which are responsible for, or contribute to, this high mortality rate, and to find means for its reduction.

Of the 56 patients who recovered, 25, or 44.6 per cent, were those in whom the placenta was easily removed, and 17, or 30.3 per cent, were in patients in whom no attempt was made to remove the placenta. Thus a total of 75 per cent of the recoveries were in these two groups.

Seven patients in these two groups (49 cases) died, a mortality rate of 14 per cent, but there was only 1 death among those patients in whom the abdomen was closed without packing or drainage, a rate of 2 per cent.

There were 5 deaths among those patients (22) in whom no attempt was made to remove the placenta, or a rate of 22.7 per cent, but they were *all* in those patients in whom the placenta was marsupialized, or in whom drainage was employed. In this subgroup, the mortality rate was 50 per cent. There was no recorded death among the patients in whom no attempt was made to remove the placenta, and in whom the abdomen was closed without drainage.

The death rate for the patients (36) in whom the placenta was removed completely, without regard to difficulty, was 11 per cent, but it was only 7 per cent in the patients (27) in whom it was specified that the placenta was easily removed.

The question of drainage of the abdomen deserves special attention. Of the 13 deaths, 11, or over 84 per cent, occurred in those patients in whom packing or drainage of the abdomen was done, and 16, or 80 per cent, of the long and complicated recoveries occurred in this division.

On the other hand, there were 33 patients in whom the postoperative convalescence was rapid and uncomplicated, and of these, 30, or 91 per cent, occurred in those patients in whom no packing or drainage was used.

It is realized that this may also be interpreted to mean that perhaps packing or drainage was used only in the most serious cases, and that since only in the less serious ones was the abdomen closed without drainage, obviously the greatest number of uncomplicated and rapid recoveries, and the smallest number of deaths occurred in the latter group.

Several observations refute this conclusion. It is noted that there were *no* deaths in the group in which no attempt was made to remove the placenta, and in which the abdomen was closed without drainage. On the other hand, the greatest number of deaths of all the groups occurred in those in which no attempt was made to remove the placenta, but in which the placenta was marsupialized, or in which drainage was employed. The matter of an open or tightly closed abdomen in this group is the only analyzable difference.

Again, in the group in which the placenta was *easily* removed, and in which no drainage was employed, there is the highest number and per-

this difficult in some cases, and later began making a small opening in the peritoneum to see exactly what he was doing. Finally, he adopted Frank's method of peritoneal exclusion.

In 1939, Waters presented a series of 42 cases in which he followed an extra-peritoneal procedure, inadvertently opening the peritoneum in only 8 of them.

Steele and Burns (1930) in their series of Latzko operations admit perforation of the peritoneum in a number of cases, but without serious consequences. Aldridge (1937) in his series of Latzko operations advises opening the peritoneum in certain cases and resuturing the superior angle in order to allow more room for the original longitudinal cervical incision of the Latzko technique.

Monroe Kerr (1937) in his book asks the question: "Does the operation (Latzko) give better results in infected cases than the simpler procedure in which the general peritoneal cavity is shut off with gauze or the visceral and parietal layers of peritoneum are stitched or clamped?" He answers this question by expressing doubt about the extensive dissection of flaps and the opening of loose connective tissue, with the risk of devitalizing peritoneum and injuring urinary structures in presumably infected cases, and further says that only the light of experience will settle the question.

In the Veit-Fromme-Hirst (1914) exclusion operation also described by Broadhead (1923) and Irving (1937), the peritoneum is likely to tear in the midline, the uterus being definitely fixed to the anterior abdominal wall by later adhesions. Cases of subsequent endometriosis of the abdominal scar after this operation have been seen by several observers. Frost (1938) recently published the description of a technique resembling that of Frank or Pfannenstiel—B. C. Hirst—Kerr (1939) peritoneal exclusion operation, which provides a sutured ring of parieto-visceral peritoneum through which the baby's head must pass, sometimes also with a laceration of the peritoneum which causes an initial amniotic spill.

There is an important disadvantage of such operations, well exemplified in a case I observed in which the Frank technique had been used. This patient, in 1937, three months after the cesarean section, required an emergency operation necessitated by a loop of intestine strangulating through the artificial internal ring or canal which is formed by the closure of the lower angle of the incision. Impressed by this accident, a technique resembling Sellheim's (1908) second method was followed in an effort to do a very low operation with exclusion features, to eliminate abdominal adhesive bands, to forestall initial tear and spill, to lessen trauma to the bladder and avoid the creation of a large area of devitalized peritoneum, and last, to keep the operative site away from the ureters and bladder bed, placing it in the well-oriented lower peritoneal cavity. The transition of an operator's technique from the low flap, such as Krönig, DeLee and Beck advocate, to this exclusion operation should be easy and accomplished with less apprehension than a Latzko operation involves. In definitely or potentially infected cases, a midline, instead of a Pfannenstiel, incision may be advisable because of its better healing in the presence of infection, but this does not affect the ease of operation. Having performed this operation on several patients not in labor, as well as those who had a trial labor, I venture to offer it as a method for elective as well as infected cases and believe that it is safer than either a classical or low flap operation.

#### TECHNIQUE

Basal anesthesia is now an established procedure, regardless of whether local, spinal or general anesthesia is selected. The barbiturates are relatively harmless

## TRANSCERVICAL CESAREAN SECTION WITH PERITONEAL EXCLUSION AND BLADDER MOBILIZATION\*

ERWIN FLETCHER SMITH, B.A., M.D., F.A.C.S., NEW YORK, N. Y.

THE cesarean section operation, executed for proper indications, will be considered in this presentation only from the standpoint of a technique which contributes to its safety. Although the question of whether or not too many cesarean sections are done is not under discussion, the fact that these operations are performed in great numbers does have vital consequences. The relatively large number of high and midclassical operations throughout the country are responsible for mortality rates that may be somewhat reduced by every improvement in technical details. In the past, deficiencies in anesthesia and surgical training were severe handicaps and, for some operators, were largely responsible for the popularity of the high operation. With the improvement in anesthetic methods, skillful administration of ethylene and cyclopropane, the more prevalent use of local anesthesia, and a better conception of the judicious application of spinal anesthesia, the operating time can be prolonged to one hour if necessary without incurring undue hazards. It is quite evident from opinions expressed in the literature, as well as from mortality and morbidity statistics, that the lower uterine segment operations provide a wider margin of safety than the classical methods, and it is therefore quite natural that obstetricians are constantly striving to develop a more satisfactory and safer technique which can be utilized generally.

In 1805, Ossiander, of Goettingen, originated the principle on which all of the present low cervical operations are based. He reasoned that hemorrhage and sepsis might be circumvented or lessened if the fetal head could be fixed against the abdominal wall with one hand in the vagina while the incision was being made. Ossiander cut alongside the pyramidalis muscle and necessarily entered the lower uterine segment. Even at this early date, he insisted that such an operation should replace the classical section. True, his patients died, but not the vital idea which he left to posterity. The next year, Joerg, of Leipsig, was influenced by Boer to make a suprapubic incision, followed by an opening into the vagina or lower uterine segment, thus allowing the infant to be delivered suprapubically. Although doing this only on a cadaver, he manifested great enthusiasm for the procedure. In 1824, Ritgen blazed a new trail by attempting the first extraperitoneal low cesarean, using a flank incision. Unfortunately his patient, weakened by hemorrhage, subsequently died of sepsis. Three years later in America Physick, quoted in De Wees *Midwifery*, proposed that a transverse incision of the lower abdomen be made just above the pubes; that the peritoneum be stripped from the bladder, thus exposing the lower uterine segment for an extraperitoneal approach. Baudeloque, in 1843, tried an operation somewhat like this but with fatal results. Cianfone, Gaillard Thomas, Skene, Gillette and others attempted similar operations before the twentieth century, some of which were successful. Sellheim in 1910, at about the same time that Frank and Latzko were perfecting their operations, followed Physick's suggestion to displace the peritoneum from the bladder. He found

\*Read at a meeting of the New York Obstetrical Society, October 10, 1939.

urachus, which is found glistening in the thin peritoneum. This fascial cord is followed inferiorly as low as the avascular area permits (Fig. 3) where the abdomen is opened in the midline on top of the bladder. This incision is then extended bilaterally for a total length of 7 inches, hugging the upper edge of bladder and curving it convexly to follow around the anterior and outer margins of the bladder.

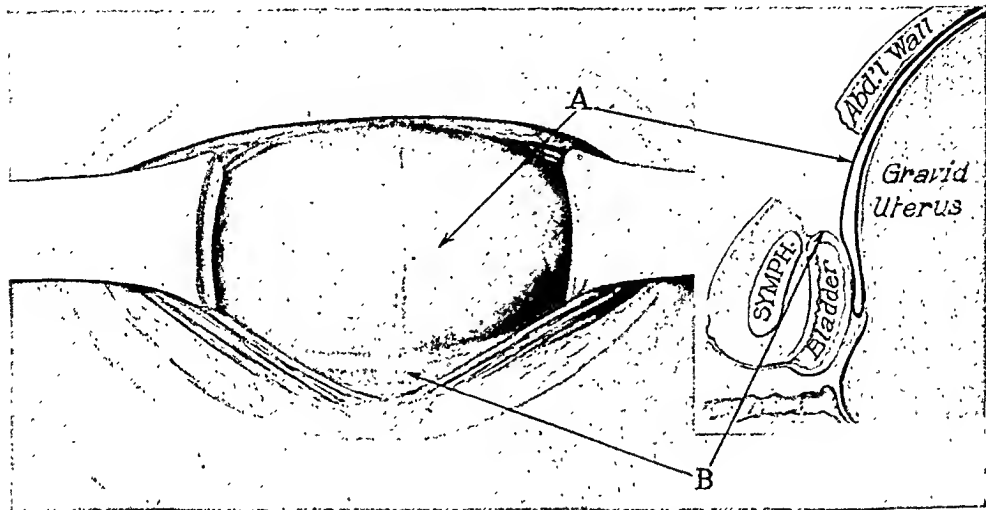


Fig. 2.—The rectus muscles retracted laterally allow the parietal peritoneum (A), fascia transversalis, and bladder (B) to balloon up, with the urachus glistening in the midline.

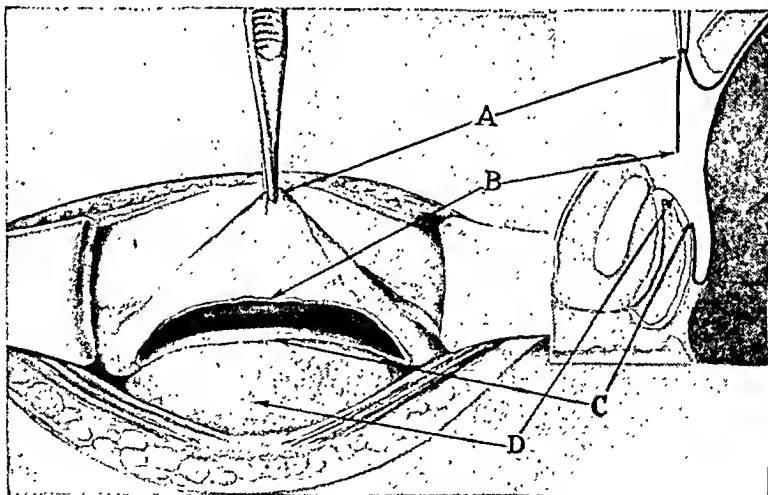


Fig. 3.—The parietal peritoneum (A) opened at B—C, cutting transversalis fascia just over bladder (D).

The lower abdominal cavity is now inspected to identify the inferior edge of the vesicouterine plica (Fig. 4). Here the visceral peritoneum is picked up, leaving as small a peritoneal strip on the bladder as possible, and it is opened transversely, again hugging the bladder with the scissors. A finger followed by a sponge stick is inserted for blunt dissection into the avascular (Fig. 4, D) region, so important in the low flap operation.

The bladder is completely freed from the cervix and pushed away from it in such a manner that the peritoneum at the posterior edges of the bladder forms a narrow ribbon strip laterally. The upper flap, as in the low flap operation, is bluntly

when correctly used, but morphine and pantopon should not be given within two hours of the abdominal delivery. The patient should be catheterized after the anesthesia is started or in the operating room while she is being prepared. Trendelenburg position is an operative aid in most cases.

A preliminary horizontal nick (Fig. 1) is made in the skin to mark the midline. Towels are then placed around the envisioned transverse incision, and fixed in position with skin clips. A  $4\frac{1}{2}$  inch Pfannenstiel incision is made 1 inch above the symphysis pubis down to the fascia. After careful hemostasis, laparotomy pads are sewn into the fat to wall off the skin. Through a small fascial opening 1 inch superior to the skin incision, the scissors are inserted and opened for lateral blunt dissection of each anterior rectus sheath, which is cut transversely for  $2\frac{1}{2}$  inches on each side. The recti muscles are separated from

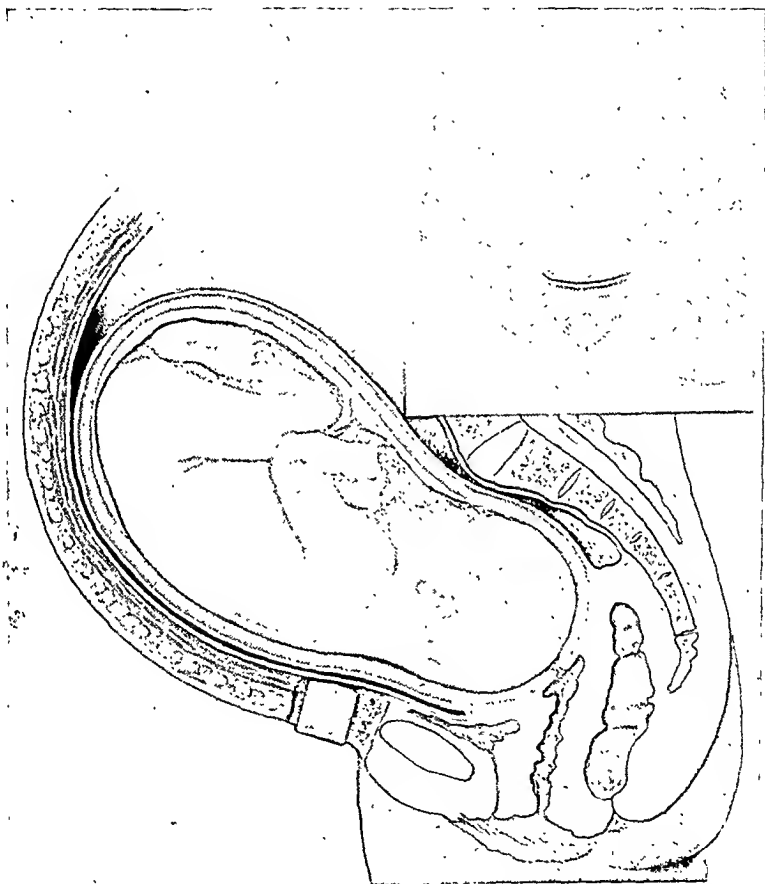


Fig. 1.—With lateral retractors in the incision, the visceral peritoneal fold over the bladder may vary in depth and contour in different cases.

their anterior fascial sheaths only on the mesial side, being careful not to create unnecessary dead space laterally. The upper and lower fascial flaps are clamped and held outward while the median raphe is cut superiorly 3 inches and inferiorly to the symphysis with scissors. Care is taken not to injure the pyramidalis muscles by dividing them evenly in the midline. With the forefingers of each hand the recti are now divulsed horizontally in the midplane and retracted laterally, which allows the transversalis fascia and peritoneum to bulge up from below (Fig. 2).

With lateral retractors, the ballooning peritoneum affords an opportunity to adapt the size of the opening to the estimated diameter of the fetal head. If this is satisfactory, search is then made through the properitoneal fat for the

suture may create a closed apex or angle. Thus the visceral and parietal layers, now approximated and forming a horseshoe, completely exclude the peritoneal cavity bilaterally and mobilize the bladder free from the abdominal cavity (Fig. 6, *D*). The closed angles which permit perfect elasticity and stretching of the suture line superiorly now drop back, exposing the lower uterine or cervical segment (Fig. 6, *B*). They form a loose, flexible peritoneal wall (Fig. 6, *A*) which will not be subject to tension during the delivery. A strip of two-inch gauze is placed over the superior flap to protect it from abrasion. The bladder, being free and mobile, is pushed under the symphysis and a retractor placed for the delivery. The raw surface of lower uterine segment is sponged with a laparotomy pad, the presenting part palpated, and the suction apparatus tested.

A one-half inch incision is made in the lower uterine segment (Fig. 6, *C*) and the suction tube inserted to drain the amniotic fluid, unless the membranes have been ruptured previously. The transverse incision, as advocated by Phaneuf, curved

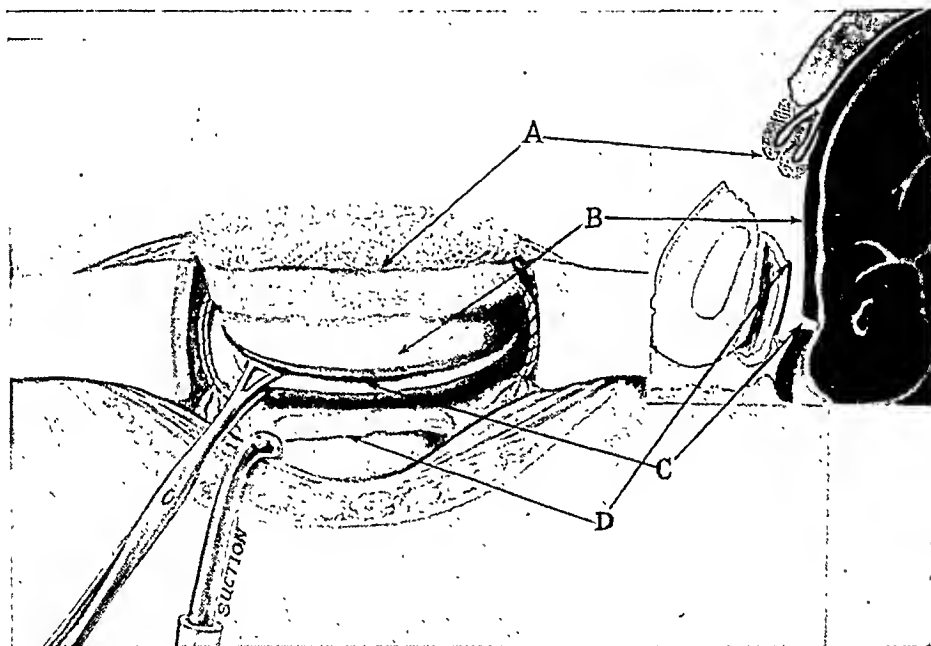


Fig. 6.—The protective gauze strip (*A*) placed over the parietovisceral peritoneum. The mobilized bladder (*D*), just before a retractor hides it under the symphysis. Lower uterine segment (*B*) above curved cervical incision (*C*).

outward and upward, is extended slowly with bandage scissors, so that all bleeding vessels may be clamped and ligated, thus keeping the field dry. Suction and laparotomy pads are both helpful, and mattress sutures may be used if necessary. Several sutures left long on the superior margin act as tractors after delivery. After removal of the initial gush of amniotic fluid and blood, by suction, the palpating hand is inserted into the incision to rotate the caput if necessary to an anterior position. This is sometimes facilitated by pushing the vertex up out of the pelvis. Some prefer to use only one blade as a vectis. In difficult cases an Allis clamp may be used to steady the head while forceps (Tucker-McLane solid blades) are applied and delivery accomplished with the aid of fundal and lateral pressure (Fig. 7). It should be emphasized that reckless speed is unnecessary, as the baby still has an attached umbilical cord. One-third grain of pantopon and 1 c.c. of pituitrin are given routinely with delivery of the infant.

Gentle traction on the previously placed tension sutures (Fig. 6, *C*) is usually sufficient to control hemorrhage, while one hand is inserted into the fundal cavity and

dissected superiorly to provide ample exposure (Fig. 4, *D*) of the lower uterine or cervical segment. The superior parietal and the visceral peritoneum (Fig. 4, *A* and *D*) are now coapted in the midline, elevated, and a running single mattress stitch is started, whose short end is caught and tied every fourth stitch, so that each single suture is continued around bilaterally until the lateral angles are reached. Here a finger is placed under the peritoneum, which comes to a ribbonlike band to cross the bladder (Fig. 5). This is freed laterally at the edge of the bladder both superiorly and inferiorly (Latzko region) and cut across (Fig. 5) so that the

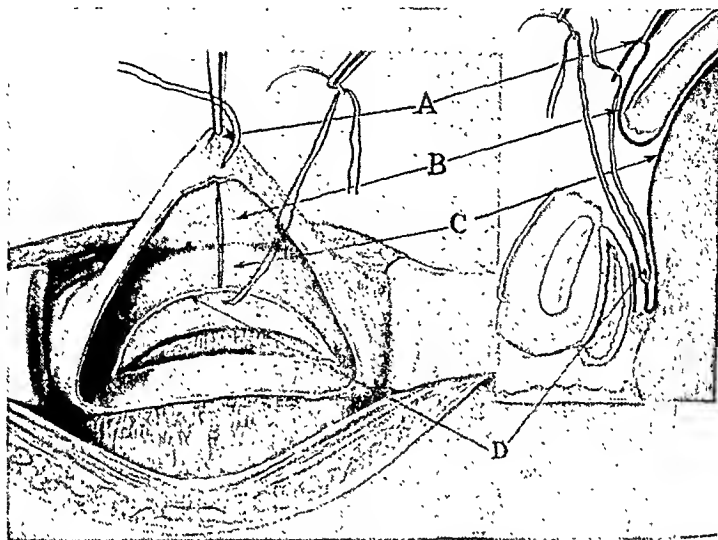


Fig. 4.—Vesicouterine fold of peritoneum (*D*) opened transversely (as in the low flap operation) and stitched to superior parietal peritoneum (*A*), to exclude peritoneal cavity (*BC*).

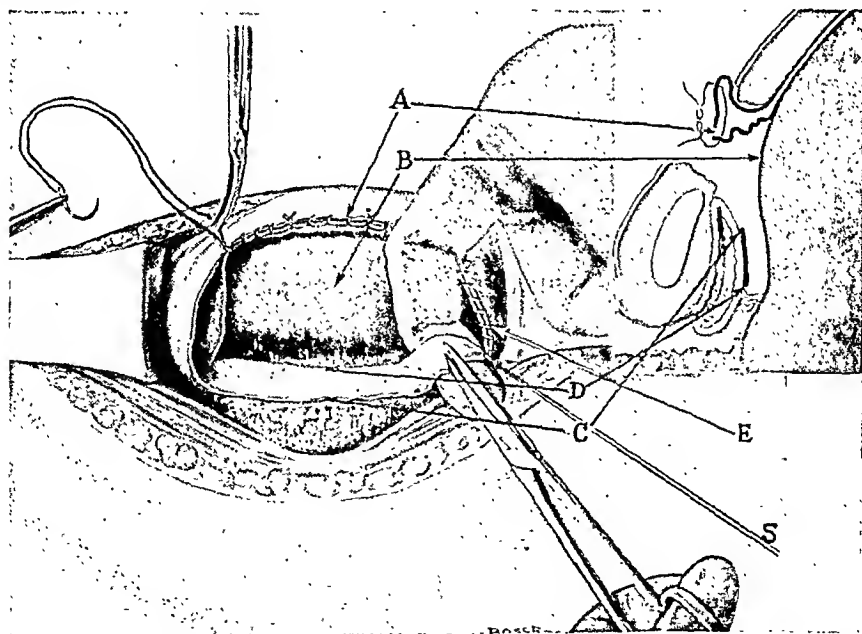


Fig. 5.—The visceral peritoneal bridge, which varies in width (*C—D*) in different cases, being cut at the closed apex of suture (*S*), after completed stitching of parieto-visceral peritoneal layers (*AE*), which then excludes bilaterally and entirely the peritoneal cavity from the lower uterine segment (*B*). [The artist has depicted the scissors cutting too far towards the midline, instead of at the apex (*S*)].



If bleeding is excessive after the third stage, hot laparotomy pads are packed into the fundus and pituitrin injected directly into the uterus. Enough of a continuous strip of 2 inch iodoform gauze is packed in the uterus to distend the fundus. Cervical dilatation with the fingers is unnecessary, as the gauze tends to soften and dilate the canal so that removal of the pack after thirty-six hours is easy. Blood clots are sponged from the soft tissues, and with traction on the primary

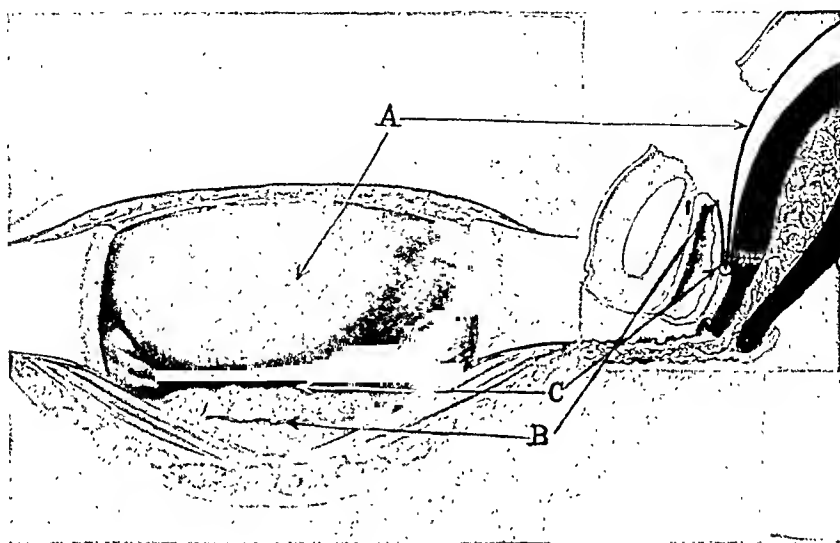


Fig. 9.—In clean cases bladder (B) may be left unsutured or may be stitched to the parietal peritoneum (A) without drainage. Insert shows uterine gauze packing.

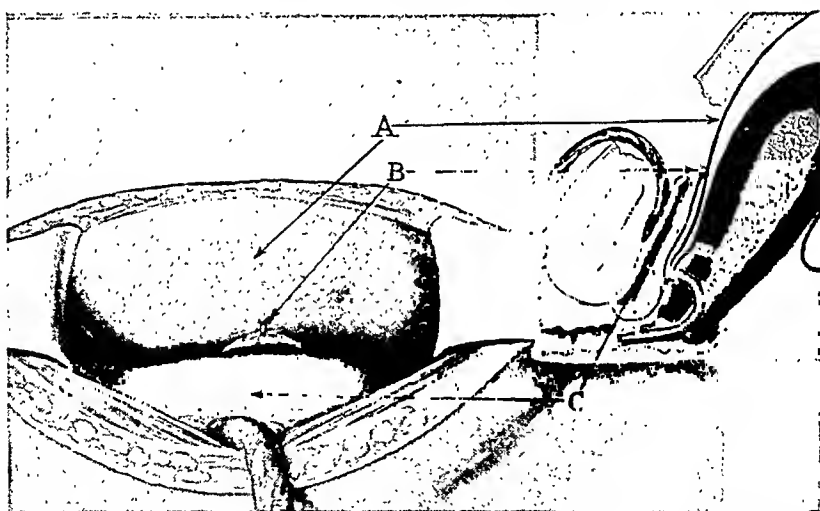


Fig. 10.—In infected cases drainage may be instituted either suprapubically, as a space of Retzius drain, or preferably through a cervical puncture, as indicated in the insert.

suture line, the incision is found contracted to one-half its normal length. It is closed with a continuous or interrupted No. 2 catgut suture, and this is then reinforced by a well-overlapped Lambert stitch which plicates the vaginal wall over the incision.

The upper peritoneal flap is now brought down (Fig. 8, A) and sewn over the cervical incision, including the lower edge of the bladder peritoneum in this closure. The upper edge of peritoneum, or bladder cap, is now attached high on the peritoneal wall to the urachus or properitoneal fat (Fig. 9, B), so that the

the other externally massages the uterus until expulsion of the placenta is accomplished. When the uterine cavity is known to be infected, however, it should not be invaded by the exploring hand. Constant pressure on the fundus after the placenta is out forces the line of incision up into full view and simplifies the closure.

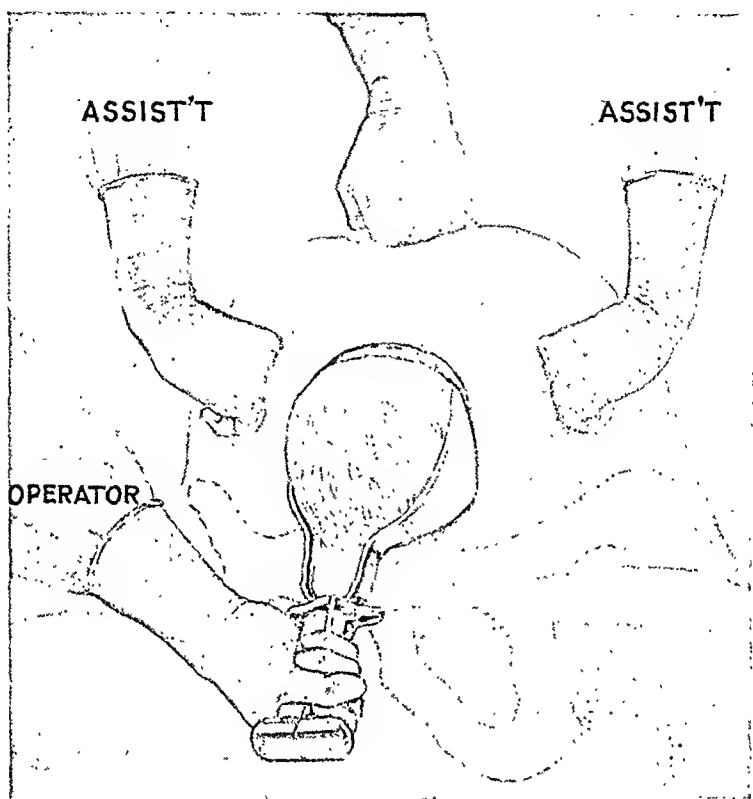


Fig. 7.—After the vertex is dislocated out of the pelvis up into the wound and forceps applied, fundal and lateral pressure facilitate the extraction.

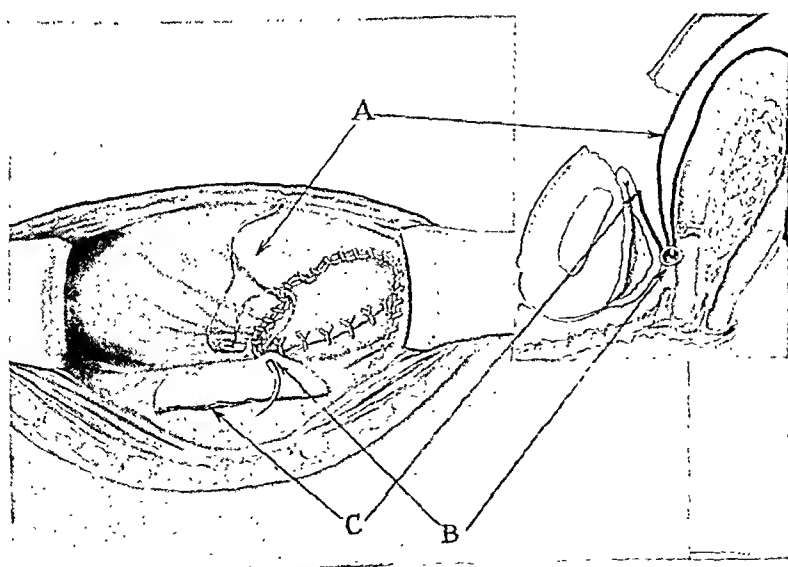


Fig. 8.—Parietovisceral fold (A) is brought down and stitched to bladder peritoneum (B), or to (C) if (BC) is too wide.

7. is equally useful in infected and noninfected cases, and is not contraindicated by breech presentation, placenta previa, and other intra-uterine complications.

### DISCUSSION

DR. LOUIS E. PHANEUF, BOSTON.—It is important to note that all the progress in the development of the lower segment cesarean section has been accomplished during the last quarter of a century. At the beginning of this period the discussion centered on whether or not the low operation was superior to the high or classical section. During the last twenty years, careful study has been given to the low operation. The two most striking recent advances are the modification of the Latzko operation by Dr. Waters, and the modification of the Veit-Fromme-Hirst technique, so-called peritoneal exclusion, which Dr. Smith has presented this evening.

Anatomically, the lower uterine segment may be reached by three methods: (1) The intraperitoneal method, which has given us the so-called low flap cesarean section, which may be done with a longitudinal incision, as advocated by Beck and DeLee, or with a transverse incision which I have preferred to use since 1926. This method may be used as an operation of election or when a test of labor has been given under clean conditions. (2) The peritoneal exclusion technique, the so-called Veit-Fromme-Hirst operation, which Dr. Smith has modified by using a transverse instead of a longitudinal incision. This is especially useful in the woman who has had a long labor and is presumably infected. The peritoneal exclusion may protect a parturient from peritonitis even when there is suppuration and a breaking down of the abdominal and cervical incisions as in a case I have observed. (3) The true extraperitoneal cesarean section, represented by the Latzko procedure and its modification by Dr. Waters, reserved usually for badly neglected and infected cases. It is interesting to me to note that in the two most recently developed techniques, those of Drs. Waters and Smith, the transverse incision in the segment has been substituted for the longitudinal or vertical.

Dr. Smith mentions three definite objections to the Veit-Fromme-Hirst operation, namely (1) fixation or the facing of the uterus to the anterior abdominal wall, (2) endometriosis in the abdominal scar, and (3) abdominal adhesive bands. The first objection is a definite one, and his operation overcomes that entirely. To me this is the most important advantage of his method. I personally have not met endometriosis of the abdominal scar as yet. I have delivered several women who had had a previous Hirst peritoneal exclusion, by the transverse cervical cesarean section, and in each instance resected the peritoneal bands, varying in width, which extended from the abdominal wall to the edge of the bladder. The second cesarean, in my experience, was not particularly difficult to do. However this may be, I can visualize Dr. Smith's procedure as preventing the formation of these bands, which may lead to intestinal strangulation, as reported in his paper. His operation impresses me as having so many advantages over the one which I have used in the past, that I know I shall adopt it in my practice.

Since Dr. Smith's operation is a form of peritoneal exclusion, I should like briefly to present my own statistics, bearing in mind that my patients were operated upon with a longitudinal incision. I have performed 70 Veit-Fromme-Hirst operations, and have delivered 71 infants, there having been one set of twins. There were 6 maternal deaths, or 8.5 per cent. In my own work this method has been reserved for those parturients who were long in labor and considered presumably infected, some of them having had attempts at delivery in their homes. In my series the longest labor was seventy-two hours. There were 7 fetal deaths in 71 children born, there being one set of twins.

DR. JAMES A. HARRAR.—It was twenty-five years ago that I heard Barton Cooke Hirst first describe his peritoneal exclusion operation at a meeting of the New York Lying-in Alumni. I had already performed a similar operation, but did not then know it was a new one.

Dr. Smith very adroitly moves the Hirst operation down from the original site to the safer lower uterine zone behind the bladder, but I think the special point

bladder is again restored to the peritoneal cavity, although it covers the incision with a double flap of peritoneum.

Drainage is not used in clean cases, but if infection is present or suspected, it may be instituted by introducing a strip of rubber dam through a stab wound in the cervix, exercising care not to retract the tissues thereafter. This method has been described and advocated by Aldridge. To drain suprapubically, a small cigarette drain is inserted in the space of Retzius (Fig. 10).

After removal of the lateral retractors, the recti muscles naturally approximate and cover the operative field, and are re-united with three interrupted mattress sutures, which are tied without tension. The fascia is closed by a continuous, locked stitch, chromic No. 2 catgut suture. The skin margins are closed with a subcuticular chromic No. 0 suture. If a suprapubic drain is used, a B & B dermal retention suture is placed on each side near the midline and tied over little gauze bolsters. A snug abdominal binder helps to restore the intra-abdominal pressure.

Pantopon, gr.  $\frac{1}{3}$ , which is given immediately after delivery of the baby, may be repeated every three or four hours as needed. The patient's position should be changed frequently. Early active movements are advisable. The bladder should be catheterized every eight hours, until there is a residual of less than 25 c.c. of urine.

#### COMMENT

Although the purpose of this communication is to describe the technical details of an operation which I hope will serve as a contribution to the safety of cesarean section, it is fair to record that in a small series of 17 cases the mothers and babies are all alive. There were no serious postoperative complications. One patient remained in the hospital twenty-seven days because of mild pulmonary complications; the others stayed ten to sixteen days. Postoperative discomfort was absent even in 2 patients with moderate distention. Seven patients were frankly infected, one having had numerous preoperative vaginal examinations and 2 attempts at forceps delivery, yet she recovered uneventfully. In another patient the uterine artery was cut and sutured with no untoward sequelae. Not a single patient had a temperature over 102° F. for more than two days, and in some the temperature rose only to 100° and dropped to normal within forty-eight hours. One patient had a placenta previa, and sutures in placental site helped to control the hemorrhage; a normal convalescence followed a single 500 c.c. postoperative transfusion. The babies were all normal, ranging in size from 5½ to 9 pounds (2,750 to 4,500 Gm.), and required a minimum of resuscitative measures.

#### SUMMARY

A technique for cesarean section has been described which:

1. affords a more roomy elastic area than any of the other exclusion operations,
2. precludes the formation of postoperative adhesive bands,
3. eliminates the possibility of subsequent intra-abdominal hernia,
4. minimizes trauma to the bladder and preserves the nutrition of the peritoneum,
5. localizes the operative site so that the ureters and bladder are not jeopardized,
6. restricts the operation to the well-oriented lower peritoneal cavity, yet provides complete peritoneal exclusion,

In view of the procedures which have been developed in the past few years to prevent contamination of the peritoneal cavity, there seems little excuse for subjecting an infected or potentially infected patient to the additional risk of a transperitoneal operation when conditions demand that she be delivered by the suprapubic route. An operation which successfully excludes the general peritoneal cavity is a step forward, but it seems certain that some type of extraperitoneal operation will eventually be accepted as the proper procedure for such a case.

At the Woman's Hospital, we have done approximately 50 extraperitoneal operations with but one maternal death. This death was due to embolism in a patient whose temperature was normal and who appeared to be doing well.

Obstetricians have little opportunity to familiarize themselves with the extraperitoneal technique because so few cases demand such treatment. Experience has proved that the technique of this operation is not too difficult and that it can be easily and safely carried out by those who have had training and experience in operative gynecology.

DR. EDWARD G. WATERS.—There is no comparison between the morbidity and, in the long run, the mortality following classical section as compared with a lower uterine segment operation. The safety of the low transverse cervical segment incision, especially as popularized by Phaneuf and Irving in Boston, and more recently in other parts of the country, has been repeatedly impressed upon my mind. In a group of 25 ruptures of the uterus which we have encountered in the past eight years, 5 of them followed classical cesarean section. One case is worth recounting. This was a patient who had had a classical cesarean section operation, then a low transverse cervical segment operation and then a third pregnancy. She ruptured her uterus at the site of the initial classical section scar.

The question arises as to whether an exclusion operation offers any special advantages; whether it is easier, or as safe as a true extraperitoneal operation. I still think the technique Dr. Smith has evolved lacks the safety, ease, and speed of a true extraperitoneal operation. With Dr. Smith's operation, by the time the uterus is opened we have an occluded peritoneal surface, but it is one which has suffered multiple needle punctures during suturing, and we are relying upon it to bar bacterial extension of infection from the to-be-infected wound area to the general peritoneal cavity. If one can go a little further than Dr. Smith and can make the operation *completely* extraperitoneal, without added hazard to the mother or baby, I think that is far preferable.

I think the exclusion operation is an advance over the low transverse cervical segment incision operation, just as that was an advance over the classical operation. But I believe you should go the whole distance and keep the operation entirely extraperitoneal.

I thought the principle of operation which I had the privilege of presenting here last January was new, but on working back in the literature, I found it to be quite old. It was first suggested to De Wees by Physick in 1824, and that is a long time ago. In struggling through the literature after doing about 20 cases, it was disclosed that a similar approach was attempted by other operators, but they failed to follow certain well-defined, we think, anatomic facts in making the operation truly extraperitoneal. This was the experience of Frank, Sellheim, and others.

With one exception, in our series of more than 70 cases several accidental peritoneal punctures occurred *before* the uterus was opened. This is an important point because the field you are operating in is still bacteriologically clean. These openings are usually small and are picked up and immediately *tied* off (not sutured with a needle) and then the operation proceeds. With one exception, we have not opened the peritoneum *subsequent* to opening the uterus, which makes it truly an extraperitoneal operation. As yet, I have not injured the bladder but expect to at some time or other. However, as you know, bladder injuries are repaired without too much difficulty by inversion suture and heal fairly promptly.

in the success of his operations is the ingenious way in which he severs the bladder peritoneum on each side, so that after the visceral and parietal peritoneum are sutured, together with his complete mobilization of the bladder superiorly and, especially, laterally, he secures a very elastic opening, through which he may extract the baby.

DR. SAMUEL A. COSGROVE.—Dr. Smith has presented an exceedingly careful, meticulously worked-out combination procedure to expose the best part of the uterus, through the peritoneal cavity, but absolutely protecting the latter. If I may be permitted to use one of his slides, however, I would like to point out what I think is the superiority of an operation that I am naturally prejudiced in favor of, since it was developed in our own clinic.

Dr. Smith in his opening remarks included our operation with all the older types that attempt to go through the lower uterine segment extraperitoneally, by saying that Dr. Waters had in his reported series of cases a few injuries of the peritoneum. In that series we also have had a few injuries of the bladder, one or two of which I have been responsible for. But I feel it is more desirable, in spite of occasional accident, to make the approach truly extraperitoneal.

I think you will recall the slide in which Dr. Smith showed a division of the lateral strands of peritoneum from the bladder. At that stage of his operation, just before he ties his exclusion suture, you will note that he has denuded the entire posterior surface of the bladder of peritoneum, and the anterior surface of the bladder has been freed; and by a clever and, so far as I know, original attempt to insure that there be no opportunity for herniation after the exclusion, he divides the peritoneum at the upper outer angle of the bladder, and includes this little flap in with his suture. Now, that is a very critical part of his technique.

Dr. Waters, by an approach from below and by a technique certainly no more difficult or time-consuming than Dr. Smith's, has first denuded the anterior surface of the bladder, then successively denuded the lateral aspect, the posterior surface and the fundus, approximately to the midline.

Both methods therefore give approximately the same mobilization and extent of peritoneal denudation of the bladder, and similar exposure of the lower uterine segment, but, whereas Dr. Smith has a half circle of incised and artificially closed peritoneum about his field, Dr. Waters provides an intact peritoneum. There is an equal amount of room between the uterine incision and peritoneal apron in both cases. The peritoneal apron is just as unsusceptible of injury in the extraction of the baby's head in one technique as in the other. The outstanding advantage of the Waters technique over the other is that the peritoneal apron is intact, and relatively untraumatized.

If the peritoneum be accidentally opened in the Waters technique, however, it is always a small rent, as compared to the extensive incision thereof made in the Smith technique. It, like the incision of the peritoneum in Dr. Smith's operation, may be sutured before the uterus is opened. If this is done, we have a short line of such suture closing the peritoneal cavity, instead of the long line of similar suture used in the Smith technique.

DR. ALBERT H. ALDRIDGE.—If any exclusion operation is to satisfy the purpose for which it is intended, the line of suture between the visceral and parietal peritoneum must be such that it will not allow contamination of the general peritoneal cavity either before or after delivery of the baby.

Following delivery, the body of the uterus normally undergoes firm contraction and marked reduction in size, and the entire organ becomes freely movable. Some of the exclusion techniques that have been described and especially those used to exclude an incision in the body of the uterus, may fail because the peritoneal suture line is much distorted after delivery. Furthermore, manipulation necessary to deliver the baby and placenta may place so much tension on the sutured peritoneal margins that they may be accidentally torn.

The exclusion technique just recommended is more likely to succeed than some of those previously described because the procedure utilizes the loose peritoneal folds about the bladder and lower uterine segment. It also takes advantage of the established benefits of uterine incision in the lower segment.

## THE ADVANTAGES OF VAGINAL APPROACH TO PELVIC PATHOLOGY\*

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*(From the Gynecological Departments of St. Luke's and Children's and Northern Liberties Hospitals)*

THE nature and extent of pelvic pathology is determined, in most part, by vaginal examinations. It was logical, then, for the early gynecologists to adopt and develop the vaginal approach in the surgical treatment of diseases of the pelvis. There was born a great American school of vaginal surgery, limited in its beginning to the simplest of plastic operations and to the puncture of a pelvic abscess, but developing to a degree that the most extensive vaginal hysterectomies were the goal in all good clinics. With the perfecting of the abdominal section, it was natural that the adventurous spirit of the surgeon led him to forego the tried fields of vaginal surgery to explore the newer field of the abdominal cavity. Times made him an abdominal surgeon, and except for plastic work, vaginal surgery was almost entirely neglected. When the gynecologist started performing abdominal surgery he soon found that he must perfect his diagnostic skill and operative technique to cope successfully with all surgical conditions of that cavity. This era marked the passing of the gynecologist and the general surgeon, though neither would admit it, and the birth of abdominal surgery as a distinct specialty.

When people became appendicitis conscious, the removal of a non-offending appendix in the course of any abdominal operation became a required routine. As a matter of fact, the statement that "the appendix will be removed at the same time" was often the determining factor in obtaining consent to an operation. This type of prophylactic surgery grew in popularity, and we soon saw the abdominal surgeon enlarging the incision, exploring every corner of the cavity in a search for pathology that could be removed. This was the era of ill-advised multiple operations, but it chained the gynecologist to the abdominal surgery.

Fortunately a few clinics kept alive interest in vaginal approach to pelvic pathology, so that when the question arose as to the virtue of total versus subtotal hysterectomy, vaginal surgeons had the correct answer. Consequently, a great impetus in the interest in and application of vaginal hysterectomy resulted. Abdominal surgeons were compelled to meet this challenge, and consequently there has been a marked advancement in technique with a lowering of a former prohibitive mortality in complete abdominal hysterectomy.

Most of the recent papers on the vaginal approach to the pelvis deal almost exclusively with hysterectomy. While hysterectomy in

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\*Read at a meeting of the Philadelphia Obstetrical Society, December 7, 1939.

I note that in the 70 cases done with the exclusion operation by Dr. Phaneuf, of the 6 maternal deaths only 2 were ascribed to local infection. We have had over 70 cases done by the extraperitoneal technique we recommend, and one patient died of heart failure while being operated upon.

DR. CLAUDE E. HEATON.—We have heard so much about the older men that perhaps it would be worth while to mention that the first three successful cases in the world were done by members of this Society. The first successful operation of the extraperitoneal variety was done by Skene of Brooklyn, the second by Gaylord Thomas at the old Nursery and Child's Hospital, and the third by Jewett of Brooklyn.

DR. GEORGE W. KOSMAK.—I cannot approve the condemnation of the old classical cesarean section.

It may be that the low flap and various other ways of entering the uterus are desirable. Yet it seems to me that the indications are limited to a comparatively small group of cases. We should select the cases more carefully in which these various types of operation are to be done. If we avoid the conditions which require these procedures, we will probably get better results with the classical cesarean section.

The classical cesarean is done rapidly and can be done without much difficulty by most operators. Especially if an incision higher in the abdomen is employed there rarely develop any adhesions between the uterus and the abdominal wall, because the uterus sinks very promptly.

The classical cesarean section offers a special facility in sterilization by tying off the tubes. It is my belief that no woman should have more than two or possibly three sections.

DR. SMITH (closing).—Recently I have performed 6 transcervical extraperitoneal operations in potentially infected cases, as advocated by Dr. Cosgrove, without entering the peritoneal cavity, but in 2 of them I accidentally opened the bladder. In these 6 cases I found that the operating time was increased from the usual thirty minutes to about an hour, probably because of the extraordinary care exercised in completely detaching the peritoneum from the bladder. There was little difference in the postoperative comfort and morbidity in these cases and those in which I used the technique described in my paper. I do believe that if one can do the extraperitoneal operation rapidly and without injury to the peritoneum or bladder, it is an excellent procedure in infected cases; but I also think that if the peritoneum is accidentally opened, considerable time may be saved by converting the operation into a peritoneal exclusion, and omitting the complete dissection of the peritoneum from the bladder because, as Dr. Waters has stated, the peritoneal cavity is closed before the infected uterus is opened.

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Tausch, M.: *Endometriosis Externa With Consideration of Cases of Unusual Localization*, Arch. f. Gynäk. 168: 8, 1939.

A number of cases of endometriosis are reported and described in detail. The author reports several cases where endometriosis was found in the abdominal wall, the umbilicus, and drainage wounds following appendectomy, and the fossa ovalis femoralis. The author concludes after a careful analysis of these cases that in them the endometriosis probably was transmitted by way of the lymphatics rather than by direct extension, implantation, or heterotopy.

RALPH A. REIS.



TABLE II. PRIMARY OPERATIONS

Vaginal hysterectomies	964
Salpingectomies for tubal pregnancy	24
Myomectomies	12
Sterilization	8
Shortening of round ligaments	10
Ovarian cystectomies	32

TABLE III. ADDITIONAL OPERATIVE PROCEDURES

Removal of one or both tubes	130
Removal of one or both ovaries	153
Plastic on urethra for incontinence	64
Posterior colpoperineorrhaphy	780
Repair of complete perineal tear	4
Preliminary episiotomy	62
Removal of Bartholin cyst	5
Repair of inguinal hernia	6
Repair of umbilical hernia	5
Appendectomy	8
Anterior colporrhaphy	8

TABLE IV. POSTOPERATIVE COMPLICATIONS

Temperature over 100.6° F. for one or more days due to:	
Femoral thrombophlebitis	12
Cystitis	58
Probably due to wound infection, low grade	170
Tonsillitis	4
Bronchitis	12
Uremia and pneumonia	1
Peritonitis	1
Deaths	3

We feel that this experience is extensive and varied enough to warrant certain conclusions:

As a general proposition, vaginal section is superior to the abdominal in that it carries a lower mortality and morbidity rate. This is proved by a study of comparative statistics and by our own experience. There were three deaths in our series, a patient mortality rate of 0.28 per cent. Naturally we saw to it that the patients were put in the best operable condition possible, but in no sense were these cases hand-picked. The character and extent of pathology was on a par with any similar number of patients operated upon in any exclusively abdominal clinic. As we presented the subject of vaginal hysterectomy before this Society several years ago, we will not discuss that phase of the subject except to reiterate that another advantage of vaginal section is that, when a hysterectomy is done, it is always a complete one. One of the pleasantest experiences with the operation is the extreme satisfaction of the patients. The absence of an incision and scar, the postoperative comfort and the rapid convalescence, are important considerations, but what is more advantageous is that the patient does not have to face the possibility of adhesions and incisional hernia.

Inhalation anesthesia and the Trendelenburg position are never necessary, so that postoperative pulmonary complications seldom oc-

our series is the most frequently performed operation, it is the purpose of this communication to consider the vaginal approach in a broader sense and to show its advantages in attacking, with certain exceptions, most pelvic pathology.

To make our position clear and to avoid any misconception of our theses, it should be stated that we are in no sense condemning abdominal section or suggesting that it should be abandoned for the vaginal approach. While we are enthusiastic as to the vaginal operation, and as our experience grows we use it more and more, our abdominal operations still exceed those done by vaginal route. Vaginal operations have their advantages, but at the same time their limitations. It may seem heretical to those who operate only by the abdominal approach, but the same statement is applicable to abdominal section. As a matter of sheer truth, one does not enter into competition with the other. Each has its indications and to use one when the interest of the patient dictates the other is poor surgery. To paraphrase Richardson: A gynecic surgeon should exact of himself and his staff as a minimum standard of skill, a mastery of a technique to approach with equal facility, the pelvis by either the abdominal or vaginal route.

This study is based on an experience of 1,060 patients operated upon by the vaginal approach. The indications for operation, the primary and additional operative procedures together with the morbidity and mortality are shown in Tables I to IV.

TABLE I. INDICATIONS FOR OPERATION AND ASSOCIATED PELVIC PATHOLOGY ENCOUNTERED

Adenomyoma of the uterus	2
Badly lacerated diseased cervix in or about the menopause	32
Chorionepithelioma of the uterus	1
Carcinoma of body of uterus	6
Fibromyoma of the uterus	625
Fibromyoma of the uterus fixed to anterior abdominal wall by previous operation	11
Fibromyoma of the uterus and bilateral chocolate cysts of ovaries	8
Fibromyoma of the uterus and ovarian tumors	28
Fibromyoma of the uterus and chronic bilateral tubo-ovarian disease	37
Hyperplastic or fibrotic uteri with excessive bleeding about the menopause	129
Ovarian cysts	
Serous	14
Dermoid	8
Twisted on pedicle	10
Prolapse of uterus	100
Prolapse of uterus with carcinoma of cervix	3
Prolapse of uterus after an interposition operation	4
Retroversion of uterus	10
Sterilizations	8
Tubal pregnancies	
Ruptured	8
Tubal abortions	11
Unruptured	5

that the best operation should be selected; for example, retrodisplacement of the uterus. It will be noted in our series that the round ligaments were shortened ten times. In these cases the recession of the uterus was not complete, and the operations were done in connection with vaginal plastic surgery. During the same period, we operated upon many more such patients through a Pfannenstiel incision, because we believe that the best operations for the correction of this lesion can satisfactorily be performed only through an abdominal approach.

Our experience has also taught us that when reconstructive surgery is required on the ovaries, tubes, or uterus, better exposure which facilitates the operation can be secured through the abdominal incision. This is definitely true as regards the tubes and ovaries, but only relatively so as regards the uterus. Our records show that 12 myomectomies were done by the vaginal route.

Thirty-two ovarian cysts were removed vaginally, but we subscribe to the surgical axiom that ovarian cysts should be removed intact, and that is best accomplished by abdominal section. That it is always so accomplished is, of course, not true, and that the cyst frequently ruptures, but that soiling, happily, is not always a fatal accident. If soiling does occur, it is less serious if it happens in the pelvic rather than in the abdominal cavity. These observations have given us the temerity to operate upon a few selected patients by the vaginal route, while subscribing to the general principle that ovarian cystic tumors are best approached by abdominal incision.

We have discussed the surgery of fibroid tumors in a previous communication. We hold as a general principle that uncomplicated tumors up to the size of a four months' pregnancy are best removed by vaginal hysterectomy. We, as well as many other surgeons, have successfully removed by morcellation much larger tumors, but some limit of general operability must be placed, so that surgical skill does not degenerate into a mere exhibition. We have tried to observe this rule and most of the 709 fibroid tumors of the uterus, removed by vaginal hysterectomy in our series, came within this category. Our large and complicated tumors were removed in most part through an abdominal incision and not infrequently by an incomplete hysterectomy. Time will not permit a discussion of other limitations and contraindications to vaginal approach, such as extensive anorectal pathology, widespread pelvic inflammatory disease, and the old endometriosis.

While our experience has taught us that vaginal section can be applied to almost all pelvic lesions, it is without a peer in solving certain definite problems. Table II shows that twenty-four ectopic pregnancies were operated on successfully through the vaginal route. A simple posterior colpotomy makes positive the diagnosis, and a slight enlargement of the incision will permit the removal of the damaged tube and the establishment of dependent drainage, as accurately, as adequately, and more safely in one-third the time than if done by abdominal section.

cur. As a matter of record, only one case of pneumonia developed in our series. For a number of years we have used spinal anesthesia, with both safety and satisfaction, almost exclusively in all our abdominal and pelvic surgery. Most of the operations in this series were done under spinal anesthesia without an anesthetic death or a morbidity traceable to the anesthetic. Rectal avertin, sacral and local anesthesia can be used with satisfaction. The wide choice of anesthesia and the lessened amount of anesthetic required was in our experience a distinct advantage in evaluating risks of operation. The safety of anesthesia and the absence of shock widen the scope of operability so we were able to operate successfully on patients, who on account of advanced age or physical disabilities, did not lend themselves to abdominal section.

It is the common experience that the majority of gynecologic patients, when operated upon, require a vaginal plastic in addition to the correction of pelvic pathology. This is to be expected, as the most common cause of pelvic pathology is childbearing. The economy in time, the safety factor and the facility of operation make for superiority of the vaginal approach when the combined operations are performed.

We have outlined, rather briefly, some of the advantages of vaginal approach to pelvic pathology under the heading of lower mortality and morbidity, complete hysterectomy, the absence of incision, wider scope of operability and choice of anesthesia, and facility in performing pelvic and vaginal plastic operations. These advantages of vaginal approach are beyond question, but to be of any real value it must be generally applicable to the correction of pelvic pathology. In our series we encountered practically all pelvic pathology commonly met with. There were 21 separate indications for operation which were met by 1,060 primary, and 1,225 additional, operations, or a total of 2,285 operative procedures. Surely such a record, with but three deaths, shows not only the scope but the safety of the vaginal approach.

We have already stated that our enthusiasm for vaginal section has not blinded us to its limitations and contraindications. As a matter of fact, surgical judgment and experience have shown that neither vaginal nor abdominal section has a universal application. All of our patients are prepared for both vaginal and abdominal approach, and often the decision as to method was not made until the patient was examined under the anesthetic.

It is the experience of all gynecologists that many of their patients present positive or suggestive abdominal pathology in addition to the pelvic lesions. While the pelvic pathology in many of these cases could be removed through the vagina, they unquestionably are best treated by abdominal section. We are decidedly against making vaginal section a bag of tricks and exploiting the legerdemain of the surgeon instead of his matured judgment.

Better results can be obtained in correcting some pelvic lesions by abdominal section, and, of course, the interest of the patient dictates

## DISCUSSION

DR. HOWARD C. TAYLOR, JR.—Dr. Averett's paper is based on over 1,000 cases so that his statistics are necessarily important. Only 3 deaths in such a series is a considerable accomplishment. There is a question, however, whether a similar group could not be treated abdominally with a similar low mortality. It must be noted that a series of cases selected for vaginal operation necessarily omits many of the most serious cases. The carcinomas of the ovary, the most difficult fibroids, and the severest cases of pelvic inflammatory disease are those which produce the greatest mortality in gynecologic surgery, and these necessarily appear only in series of abdominally treated patients. I believe that a mortality similar to that reported by Dr. Averett for the vaginal approach could be obtained by an experienced operator through the abdominal route in a similar group of cases. A possible exception is that in some older women in whom there is a grave medical risk you may be able to do the vaginal operations with a lower mortality.

I would be interested if Dr. Averett would give us an idea whether the vaginal approach is generally applicable or should be reserved for those men who have had a great operative experience? Should the vaginal technique be part of our resident teaching and should the occasional operator, who does 20 to 30 gynecologic operations a year, attempt this work or restrict himself to the simpler abdominal approach?

DR. GEORGE OUTERBRIDGE.—I wish that Dr. Averett would say more about the limitation of the size of cysts removable through the vagina and the question of adhesions, which are exceedingly common in ovarian cysts.

DR. WILLIAM R. NICHOLSON.—I cannot conceive of attempting to remove fibroids by the vaginal route. Morcellation through the vagina would, in the event of a fatality, be a good cause for a suit for malpractice, and those cases of fibroid which can be removed without morcellation through the vagina do not in many instances need operation at all.

The convalescence from abdominal hysterectomy in good hands is so simple that it is inconceivable to me why anyone should attempt to do this operation by any route except through the abdomen. There is no question that in rare cases vaginal hysterectomy has its place. The vaginal approach to pelvic inflammatory disease, to ovarian cysts, or to ectopic pregnancy is entirely unjustifiable.

DR. AVERETT (closing).—We have removed tumors the size of a six and seven months' pregnancy, but we do not recommend this as a general practice.

Cases of pelvic inflammatory disease are in the main not suited for vaginal operations, and are best treated by supravaginal hysterectomy. On the other hand, simple adhesions are not a deterrent and can be coped with as well vaginally as abdominally.

All of our patients are prepared for the abdominal as well as vaginal section, but so far we have not started an operation vaginally that we have not completed vaginally.

The size of the myoma is not so important as the associated complications. Multiple fibroids of the subserous type are as a rule not hard to remove. The intramural type, however, are at times difficult. The beginner in vaginal surgery should limit himself to the removal of the freely movable uterus, not larger than a three or four months' pregnancy. As his experience grows, he can remove the larger and more complicated pathology. Vaginal surgery is only for the man who devotes himself to extensive gynecologic surgical practice. Otherwise he will not have the experience to develop the skill required in this work.

A freely movable ovarian cyst, or when twisted on the pedicle and in the cul-de-sac, is very easily removed. As the sac comes down, and if there are adhesions, you see them and they can be resected with as much ease as through the abdomen.

Eight sterilizations were performed through a vaginal incision. This is such a minor procedure when done through the vagina that one is hardly justified in opening the abdomen when tubal sterilization is the sole indication for operation.

Nonneoplastic uterine bleeding during or near the menopause was the indication in 129 of our operations. These were all vaginal hysterectomies with or without the preservation of the ovaries, depending on the age of the patient and the ovarian activity. We have given up the use of x-ray and radium in the treatment of patients of this type. We have demonstrated that vaginal hysterectomy is as safe as irradiation, and further that hysterectomy gives complete protection against the development of cancer. When we save functioning ovaries, we are not plagued by endeavoring to control irradiation menopausal symptoms.

The cure of uterine and vaginal prolapse resolves itself into two groups: Women in the childbearing period and those beyond that period. We now limit ourselves to two operations which fully meet the requirements in these two groups: The Manchester operation in the childbearing woman and vaginal hysterectomy and vaginal-bladder interposition of the united broad ligaments in the women near or past the menopause. We no longer use the Watkins operation, because of the frequent and oftentimes serious late complications, and because the retention of the uterus is not necessary to the success of a prolapse operation. We report in this series one hundred and seven (107) cases of complete prolapse of the uterus operated on by vaginal hysterectomy and interposition of the ligaments without a death or a known failure. We are not reporting our Manchester operations as they do not come within the purview of this communication.

As a real cancer prophylactic we advocate, when the cervix is so diseased as to require a high amputation, that the whole uterus be removed. Our experience has shown, especially in women in or near the menopause, that vaginal hysterectomy can be done as safely and with far less morbidity than the high amputation. Extensive disease of the cervix was the primary indication for operation in 32 of our cases. Of course, in many of our other hysterectomies, the condition of the cervix was an additional indication for the operation.

#### SUMMARY

We report a series of 1,060 patients operated upon by vaginal section for 21 distinct pelvic lesions. In the correction of those primary lesions and associated vaginal and pelvic pathology, we did a total of 2,285 surgical procedures. Three patients died, a patient mortality of 0.28 per cent.

We have endeavored to present fairly the superiority of the operation in general, its particular value under certain conditions, and its limitation and contraindications. A perusal of the literature will show that it has never lost its popularity in European clinics, but that it is being neglected in American clinics. We hope that our experience, as well as that of other reporters, will stimulate greater interest and use of the vaginal approach to pelvic pathology.

Since many observers<sup>9-11</sup> have reported that in vaginitis better results were obtained with estrogens in the form of local suppositories, this route was utilized in vaginitis, even when characteristic vasomotor symptoms were present. Stilbestrol produced similar results as shown in the group in which the combination of suppository and hypodermic instillation was used.

### COMPLICATIONS

Untoward symptoms of estrogen medication have been reported by Schneider.<sup>12</sup> These have been ascribed to overdosage in patients showing only slight degrees of follicular deficiency. In these cases overdosage appeared to aggravate the menopausal complaints. In addition, new disturbances also appeared. In some of our cases with slight symptoms, we observed undesirable "side effects," due to overdosage (see Table IIIA).

In 20 of our 77 patients uterine bleeding, 3 to 4 pads a day, occurred, but in no case was the hemorrhage disturbing. In these 20 cases the longest period of amenorrhea had been twenty-two years and the shortest, two years. The bleeding took place between the fourth and ninth weeks in the course of treatment, especially in patients who received the larger doses. Several early menopausal

TABLE I. SYMPTOMS AND SIGNS, BEFORE TREATMENT

NUMBER		PER CENT
77	All patients	100
75	Nervousness	98
70	Flushes	91
68	Excitability	88
68	Fatigue or lassitude	88
61	Irritability	79
56	Sleep disturbances	72
46	Headache	62
28	Hypertension	36
28	Vertigo	36
27	Crying spells	35
23	Itching (vaginal)	29
22	Vaginal discharge	29
16	Sweating	21
8	Backache	10
7	Generalized or vague pains	9
6	Joint pains	8
2	Rhinitis	3

TABLE II. RESULTS

NUMBER		PER CENT
48	Majority of symptoms relieved	62
21	Partly relieved of symptoms	28
8	Not relieved or doubtful	10
77		100

TABLE IIIA. SIDE RESULTS AND COMPLICATIONS FOLLOWING EXCESSIVE DOSAGE

NUMBER		PER CENT
28	Nausea	36
24	Pelvic or ovarian pain	31
21	Headache	27
11	Vertigo	14
4	Loss of appetite	5
2	Rash at site of injection	3

Note: These side effects were controlled after downward adjustment of dosage.

## THE EFFECTS OF DI.ETHYL STILBENE (STILBESTROL) ON MENOPAUSAL SYMPTOMS\*

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**I**DENTIFICATION and synthesis of the estrogenic hormone of the ovary<sup>1</sup> have radically changed the therapy of menopausal complaints. A most recent addition to our armamentarium is the synthetic estrogenic preparation 4-4, dihydroxy-a, B-diethyl stilbene, known as "Stilbestrol."<sup>2</sup>

During a study of the relationship of estrogenic activity to carcinogenesis, Dodds<sup>3</sup> discovered that this preparation possessed estrogenic activity  $2\frac{1}{2}$  to 3 times as potent as crystalline estrone. It exhibited all the physiologic properties of natural occurring estrogens. This was confirmed by Gnlldberg,<sup>4</sup> and more recently, by the British writers, MacGregor and Winterton,<sup>5</sup> Bishop,<sup>6</sup> Kellar and Sutherland.<sup>7</sup>

### PATIENTS TREATED

Seventy-seven patients were treated with this synthetic estrogen, stilbestrol.† Forty-four, or 57 per cent, were cases of natural menopause, 25, or 33 per cent, were surgical and 8, or 10 per cent, were radium castrates.

### METHOD AND DOSAGE

Thirty-two patients received stilbestrol *hypodermically*. After much trial, it was found that 0.4 mg. three times weekly for 18 injections was adequate for the control of symptoms. Some patients responded to smaller doses, while others required quantities even up to 5 mg.

Thirteen patients were treated with *oral* medication alone, the dose ranging from 1 to 4 mg. daily. Some changes were noted soon after medication was started and the improvement continued for three to ten weeks.

In 11 patients with pruritus vulvae, the stilbestrol was administered by vaginal suppository; one in the morning and one at night for a period of from two to five weeks. Relief of the itching was noted in all but one instance.

Eleven patients with vaginitis received a combination of hypodermic medication and suppositories, the 0.1 mg. suppository being administered each evening, and the hypodermic dose of 0.2 mg. being administered three times weekly for a period of three to ten weeks. The itching was promptly relieved, with rapid changes in the vaginal epithelium. Vasomotor symptoms responded more slowly.

Ten menopausal patients were treated by a combination of oral and hypodermic methods. One milligram tablet was given each evening, and an injection of 0.2 mg. administered three times a week for a period of three to ten weeks. In these cases relief was obtained more rapidly than by oral medication alone.

\*Read at a meeting of the Clinical Society of the Newark Beth Israel Hospital, October 4, 1939.

†For the stilbestrol used in this investigation we are indebted to Dr. J. Morrell of E. R. Squibb & Son.

‡Stilbestrol was used in the form of: Tablets containing 1 mg. vaginal suppositories containing 0.1 mg.; ampoules of 0.2 mg., 1 mg., and 5 mg.



TABLE V. PERIOD OF OBSERVATION

NUMBER		PER CENT
5	Two or three weeks	6
8	Four weeks	10
17	Five weeks	22
21	Six weeks	27
6	Seven weeks	8
6	Eight weeks	8
3	Nine weeks	4
11*	Ten weeks	15
—		—
77		100

\*Last group includes most serious cases of all types.

for three weeks, though this dosage seldom caused the vaginal smears to exhibit the full estrous phase.

Patients with severe symptoms required 0.4 mg. every third day for 18 injections to produce the complete follicular smear and complete symptomatic relief.

#### EFFECTS ON TUBES

To evaluate the estrogenic effects of stilbestrol on the Fallopian tubes, Rubin tests with kymographic tracings were made in four cases.\* Comparative charts, Figs. 1 and 2, show the contrast between the atonic tubes before treatment and the subsequent increased tonicity with appearance of peristalsis after therapy. Geist<sup>14</sup> reported similar results with the natural estrogens.

#### DOSAGE REGULATION

As soon as symptoms had been controlled by the injection of 0.4 mg. of stilbestrol three times a week (requiring six to ten weeks), the dose was gradually reduced to 0.2 mg. Improvement could be maintained on this amount, as well as by oral administration of 1 mg. daily. These maintenance doses were sufficient to keep symptoms under control, but had to be continued. In this respect, it is similar to the dosage control required when natural estrogen is used<sup>11</sup> (Table V).

The suppositories were not used for maintenance after local symptoms were ameliorated. Oral therapy was the desired route for maintenance, but when there was recurrence of local symptoms, suppositories were again administered, one (0.1 mg.) each night until local symptoms again subsided.

Patients with artificial menopause usually have more severe symptoms and require larger doses than patients passing through a natural menopause. Prophylactic administration of stilbestrol in 5 cases following surgical or radium castration mitigated or prevented sudden severe symptoms of glandular imbalance.

#### RESULTS

Forty-eight of the 77 patients (62 per cent) were relieved of the majority of their symptoms. Twenty-one patients (28 per cent) were partly improved. In the remaining 8 cases (10 per cent), results were unsatisfactory (Table II).

Results were evaluated by the following criteria: disappearance of predominating menopausal symptoms, changes in vaginal smears, biopsies and kymographic tracings of tubal peristalsis.

Relief was usually striking. Flushes, chills, excitability, irritability, depression, crying spells, palpitation, and insomnia usually disappeared after six weeks of therapy (regardless of the route of administration). Sweating, fatigue, and headache were relieved after further administration of stilbestrol (Table I).

One patient had had persistent psoriasis, which cleared up whenever she reached the fourth month in a pregnancy, only to break out again a week after

\*Dr. M. Weiss's aid in making the tracings is here acknowledged.

TABLE IIIB. SIDE RESULTS AND COMPLICATIONS RESULTING FROM DOSAGE ACCUMULATION

NUMBER		PER CENT
20	Vaginal bleeding or staining	26
5	Pigmentation of nipples	6
3	Epistaxis	4
3	Fullness or pain in breasts	4
2	Cervical polyps	3

cases with irregular uterine bleeding became less profuse in quantity, and more regular in cycle. Withdrawal bleeding occurred more frequently in this type of early menopausal case.

In our original efforts, spurred by hope of securing dramatic results, we gave large doses. We found that 90 per cent of those who received tri-weekly hypodermic injections of  $2\frac{1}{2}$  mg. or more showed nausea without vomiting, pelvic pains, epistaxis, uterine hemorrhage, changes in the breasts and nipples, fatigue, vertigo, anorexia, and headache. These usually occurred after the first week of treatment. We questioned whether these effects were toxic or whether they were due to overdosage. To answer this, after an interval of four weeks, we reinstituted treatment with 0.2 mg. three times for the first week, 0.4 mg. per dose during the next week, and so on, gradually increasing each dose to 5.0 mg. By this time undesirable effects reappeared, though a few patients could comfortably tolerate the 5 mg. dosage. This seemed to confirm Schneider's hypothesis<sup>12</sup> that overdosage produced the undesirable symptoms.

#### VAGINAL SMEARS AND BIOPSIES

Vaginal smears reflect both local and general menopausal symptoms.<sup>13</sup> Smears taken at weekly intervals were used as a therapeutic guide.\* Relief from symptoms was often obtained before the complete follicular type of smear was noted, and improvement of local symptoms would occur with doses inadequate to produce complete building-up of the vaginal mucous membrane. It appears that a definite time is necessary, regardless of the size of the dose, to effect the histologic transformation from atrophic to estrous type of mucous membrane (Table IV). Vaginal biopsies in six cases showed corresponding changes.

TABLE IV. VAGINAL SMEARS

NUMBER BEFORE TREATMENT		NUMBER AFTER TREATMENT
26	Zero	1
25	Minus one	0
6	One	0
5	One-plus	0
5	Minus two	0
7	Two	0
0	Two-plus	5
0	Three	22
0	Three-plus	49
—		—
77		77

Many patients obtained relief from neurocirculatory symptoms when the smear showed only the beginning follicular phase. Nervousness, flushes, chills, sleep disturbances, crying spells, and depression, all began to improve after 8 or 9 injections of only 0.2 mg. (three times a week) or after 1 mg. tablet orally daily

\*The assistance of Dr. Wm. Antopol, Pathologist and Head of the Division of Laboratories of the Newark Beth Israel Hospital, in interpreting the smears and biopsies, as well as his helpful suggestions in the preparation of this paper, is gratefully acknowledged.

## SELECTED CASE HISTORIES

CASE 40.—R. S., aged 58 years, after passing through a natural menopause at the age of 49, developed a series of complaints including nervousness, fatigue, lassitude, excitability, irritability, and vague pains which persisted until time of treatment. She was having four flushes an hour.

On April 26, 1939, vaginal biopsy disclosed minimal cornification with no functionalis layer. Round cell collection was found in the subepithelial layers, but no mitotic figures were seen in the basalis, nor were any large clear cells found (Fig. 1, *A*). Vaginal smear was smudgy with fibrin, leucocytes and an occasional cluster of nucleated epithelial cells (Fig. 2, *A*). Tubal insufflation with kymographic tracings showed the low atonic curve of menopausal type.

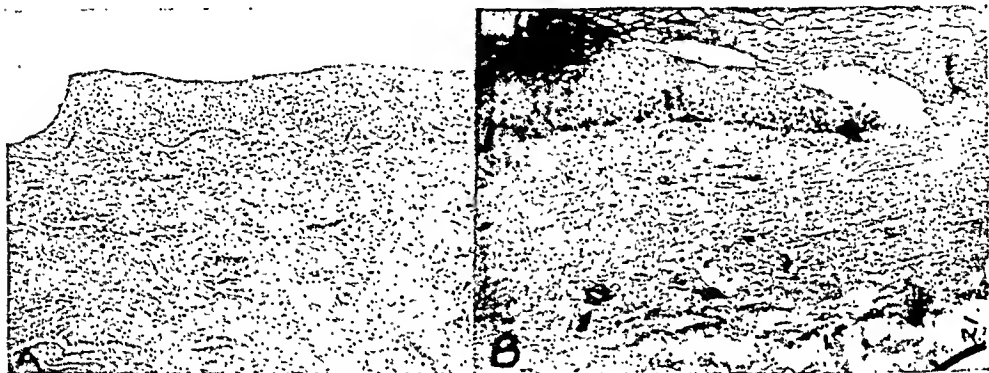


Fig. 1.—*A*, Vaginal biopsy taken at time of Fig. 2, *A*, showing minimal cornification with no functionalis layer, no mitotic figures in basalis, and no large clear epithelial cells. *B*, Vaginal biopsy taken at time of Fig. 2, *D*, showing thick epithelial layer with cornification and wide band of clear nonnucleated epithelial cells.

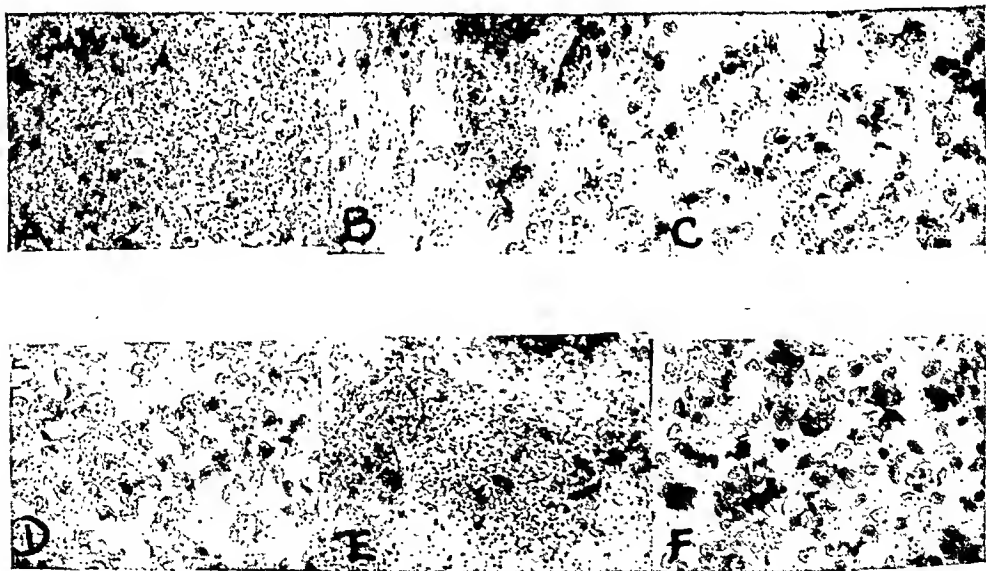


Fig. 2.—*A*, Vaginal smear taken from patient R. S., aged 58 years, nine years after menopause. Smear contains typical atrophy cells, leucocytes, and a few erythrocytes. *B*, Vaginal smear after ten days' treatment (3.6 mg. hypodermically). Smear though still smudgy shows disappearance of leucocytes. *C*, Smear after eighteen days' treatment (8.6 mg. hypodermically). Epithelial cells are larger, still have tendency to form clumps; nuclei becoming smaller and pyknotic. *D*, Smear after total stilbestrol 33.6 mg. (hypodermically) shows large clear cells, pyknotic nuclei, no leucocytes. Clinical symptoms completely relieved. *E*, Smear taken two weeks after discontinuance of treatment, showing regression. *F*, Smear three weeks after reinstitution of treatment by oral medication, 1 mg. tablet daily, indicating return to full estrous phase.

delivery. She complained that with the onset of the menopause, the psoriasis had become more widespread and more severe. After 13 mg. of stilbestrol (two and one-half weeks of hypodermic treatment) the rash began to disappear.

Two patients with atrophic rhinitis complained of dry, scaling, nasal mucous membrane, but noted marked improvement while receiving injections of large doses of stilbestrol for their menopausal complaints.

Libido improved in 20 cases. Effects of stilbestrol on the breasts were often striking. In 8 cases, the breasts enlarged and the nipples became darker in color and more erectile. In 5 of these patients this was maintained for more than a month after treatment had been discontinued. In 4, the pigmented areola became much darker.

Of 22 cases of senile vaginitis, with watery discharge, dysuria, pelvic discomfort, and pruritus vulvae, 21 patients improved. In 12 patients treated for six weeks, symptoms recurred after treatment had been discontinued. These 12 were given another course of treatment with the dosage reduced 75 per cent with resulting relief.

In 9 patients, a diagnosis of involutional melancholia had been made. In this group, best response was obtained when injections were given in larger amounts, i.e.,  $2\frac{1}{2}$  to 5 mg. three times a week. Six patients, receiving  $2\frac{1}{2}$  mg. and over, three times a week for eight to ten weeks, showed definite improvement. One, receiving 0.2 mg. to 1 mg. three times a week, did not improve. Two patients, receiving 16 and 18 mg. (total dosage) over a period of six weeks, showed only slight improvement. Sleep disturbances improved first, then there were fewer crying spells, and a gradual improvement in nervousness, depression, and "jitters." This group tolerated large doses of stilbestrol.

Hypertension was observed in 28 cases. In 9 the blood pressure was appreciably lowered after stilbestrol administration. In 6 of these the fall was from 200 and over to 160 mm. during treatment. The remaining 19 patients showed no improvement in the hypertension.

#### REGRESSION

When treatment was withdrawn after initial relief, symptoms recurred in 60 of the 77 cases (78 per cent). Complete regression as noted by the smears, occurred within a month, though the symptoms were milder than those of the original pretreatment syndrome. Most of these patients then received oral therapy until they became symptom-free, and then the dosage was reduced. Vaginal smears during these withdrawal stages showed slow regression of the follicular phase to the nonestrous phase with gradual reappearance of vasomotor symptoms. With reinstitution of oral therapy, a regeneration of the vaginal mucous membrane took place, smears of the follicular phase reappeared and the patient again became symptom-free.

#### COMMENT

Natural estrogen therapy has given new hope to the distressed and large army of menopausal sufferers. For any new synthetic estrogen now to merit acceptance, it must prove its superiority over the natural product in the treatment of a variety of conditions, such as vaginitis, leucoplakia vulvae, and the menopausal syndrome generally, and in addition, must also demonstrate some advantage in convenience of administration or cost. If it can fulfill these requirements, its value in clinical gynecology will be considerable.

Our results with synthetic estrogen have been encouraging and tentatively seem to conform with these desiderata. However, due to the preliminary nature of these observations, the brevity of our observation periods, and the relatively small number of cases here reported, we feel that stilbestrol must still be regarded as an experimental preparation.

On May 28, slight vaginal staining appeared. This complication which lasted only for the day was accompanied by ovarian pain and backache. Biopsy on June 5 indicated that the epithelial layer was much thicker with slight cornification and a wide band of clear, large, nonnucleated cells. Cellular infiltration was absent except near the site of the first biopsy (Fig. 1, *B*). Vaginal smear showed large, clear cells, many with pyknotic nuclei, but no leucocytes were seen. The total stilbestrol administration now had reached 33.6 mg. Flushes had ceased, and there was definite feeling of well-being (Fig. 2, *D*).

On June 6, all medication was discontinued, but on June 22, vaginal smear showed regression (Fig. 2, *E*). Flushes and fatigue had returned, and treatment, this time by mouth, was resumed. Between June 23 and July 13, 1 mg. tablet was taken every day, and by July 13, the flushes were quite under control, and the smear indicated a return of full estrous phase (Fig. 2, *F*).

CASE 2.—M. J., aged 55 years, passed through her natural menopause at the age of 47. She complained now of aching pains, nervousness, insomnia, irritability, poor memory, fatigue, and itching vaginal discharge; and she experienced about 10 flushes a day. Vaginal smear, taken April 11, 1939, showed chiefly small cells with comparatively few epithelial cells, a typical menopausal picture (Fig. 3, *A*). An insufflation test with kymographic tracings revealed atonic curve with no peristalsis.

Treatment consisted of daily administration of two suppositories, each containing 0.1 mg. of stilbestrol, and of triweekly injection of 0.2 mg. of the estrogen. After a week of treatment, the itching was relieved, and the smear showed predominance of epithelial cells, some leucocytes being present (2-plus) (Fig. 3, *B*).

May 4, a vaginal smear showed large, clear epithelial cells with few leucocytes (Fig. 3, *C*).

On May 15, a Rubin test revealed marked estrogenic effects on the tubes; peristalsis and increased tubal tonicity were noted on the kymographic tracings. The smear was free of leucocytes (Fig. 3, *D*). Aggregate dosage to this point had been 3 mg. hypodermically and 7 mg. by suppository.

Fairly profuse bleeding appeared on May 17. Treatment was then discontinued, and the bleeding ceased on May 24. Vaginal smear taken June 1 showed bleeding (Fig. 3, *E*). By June 19 (five weeks after last treatment), the smear showed regression but vasomotor symptoms had not recurred (Fig. 3, *F*).

CASE 26.—L. S., aged 52 years, following a surgical menopause at the age of 48, developed, and still had, the usual menopausal symptoms: flushes, excitability, headache, nervousness, insomnia, and night sweats. A menopausal type vaginal smear disclosed numerous leucocytes and epithelial cells (Fig. 4, *A*). For seven weeks, beginning April 1, 1939, 1 mg. tablet of stilbestrol was given daily. On April 18, the smear was 1-plus (i.e., it was smudgy but few leucocytes remained), showing slight estrous phase (Fig. 4, *B*). This had improved to 2-plus by May 5 (Fig. 4, *C*), but reached full estrous phase by May 19 (Fig. 4, *D*). By this time flushes and night sweats had disappeared. Treatment was discontinued on May 19. On June 2, the smear showed increase in smudginess and leucocytes (Fig. 4, *E*), and by June 15, the flushes and night sweats had returned (Fig. 4, *F*). For this reason, treatment was resumed. Symptoms were controlled by daily administration of 1 mg. of stilbestrol by mouth, and after three weeks of this, the smear was fully estrinized (Fig. 4, *G*).

### CONCLUSIONS

1. Seventy-seven menopausal patients were treated with a synthetic estrogen, "stilbestrol." Amounts necessary for complete replacement in the menopause varied from 0.2 mg. hypodermically (three times a week) to 5 mg., with the average at 0.4 mg. given three times a week for six weeks (Table V).

2. Some improvement was noted in 90 per cent of the cases, and 62 per cent of the patients exhibited improvement in a majority of all their complaints (Table II).

Treatment began May 1, consisting of 0.2 mg. of stilbestrol hypodermically three times during the first week. 1 mg. three times during the second week. By May 10, the smear, though still smudgy, showed disappearance of leucocytes. Nuclei were present in the epithelial cells (Fig. 2, B). During the next four weeks, she received  $2\frac{1}{2}$  mg. hypodermically three times a week. By May 18, the smudginess in the smear had disappeared. The cells became larger and the outlines were distinct; nuclei were small and pyknotic (Fig. 2, C). Rubin test on May 25 indicated marked peristalsis with greater tubal tonicity. By now an aggregate of 16 mg. of stilbestrol had been given.

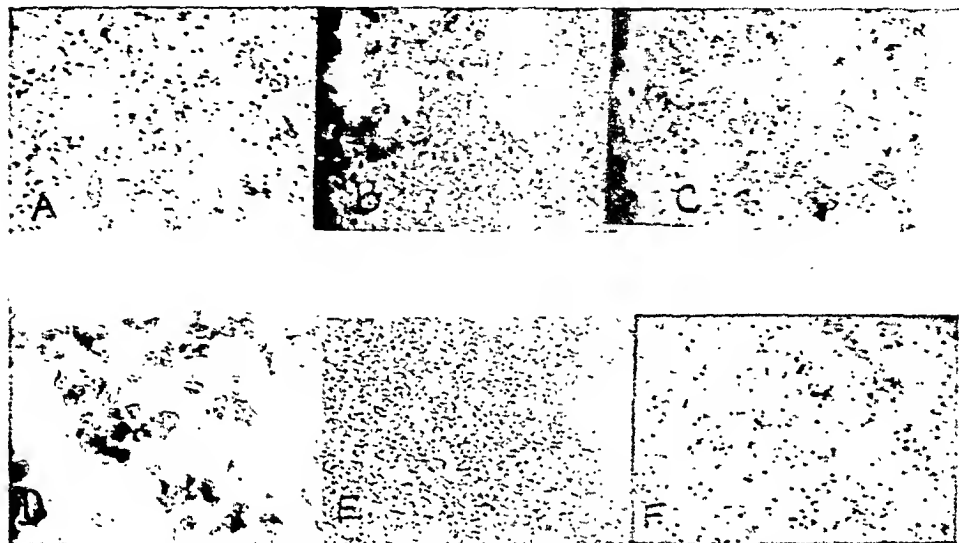


Fig. 3.—A, Vaginal smear taken from patient M. J., aged 55 years, eight years after menopause. Smear contains chiefly small cells, with comparatively few epithelial cells. B, Vaginal smear after one week, daily administration of two suppositories (each 0.1 mg. stilbestrol) and three injections of 0.2 mg., showing leucocyte grouping and predominance of epithelial cells. C, Vaginal smear after three weeks' treatment, showing large, clear epithelial cells, less tendency to form clumps. D, Smear after total stilbestrol of 3.0 mg. hypodermically and 7 mg. by suppository. Showing large clear cells, pyknotic nuclei. Symptoms completely relieved. E, Smear taken June 1, two weeks after discontinuance of treatment, showing regression. F, Smear taken five weeks after discontinuance of treatment, showing regression. Clinical symptoms had not recurred.

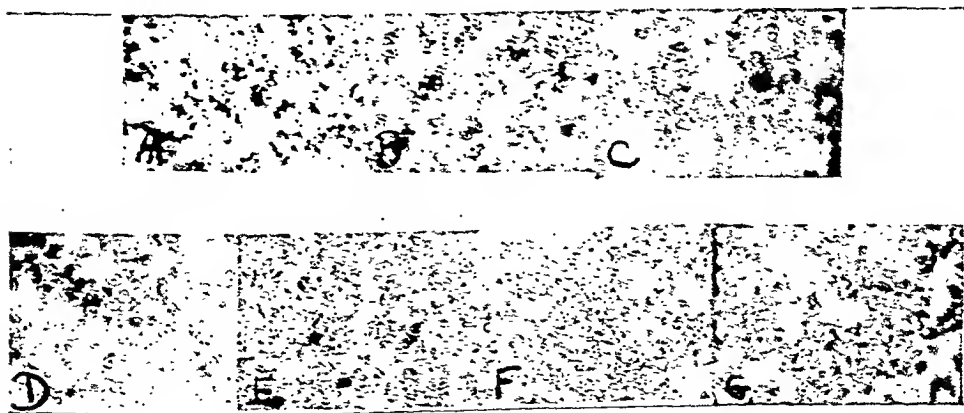


Fig. 4.—A, Vaginal smear taken from patient L. S., aged 52 years, four years after surgical menopause, showing numerous leucocytes and atrophic cells. B, Vaginal smear after two weeks' daily administration of 1.0 mg. tablet of stilbestrol, showing few leucocytes, epithelial cells vary in shape. C, Smear after four weeks' treatment, showing epithelial cells larger, no leucocytes. D, Smear after total stilbestrol of 45 mg., showing full estrous phase. Flushes and night sweats had disappeared. E, Smear two weeks after discontinuance of treatment, showing beginning regression. F, Smear one month after discontinuance of treatment, showing increased smudginess and leucocytes. Flushes and night sweats had returned. G, Smear three weeks after re-institution of daily 1 mg. oral stilbestrol, showing full estrous phase.

had been required daily during the past three years. In 1924 a local physician insufflated the vagina with a "caustic powder." After a few treatments rather profuse vaginal spotting developed. In 1926 treatment was sought from another physician who made a diagnosis of acute vaginitis. Soda douches and sitz baths were prescribed. The discharge and soreness became less, but never completely disappeared. In 1933, the acute condition recurred and dilatation and curettage were done. The curettings were reported as nonmalignant. By the summer of 1938 the vagina had become so small that a douche nozzle could not be introduced. Again in the fall of 1938 vaginal pain and soreness increased and a bloody discharge reappeared. Early in 1939 the vulva became reddened and swollen. An abscess (pyometra?) ruptured through the vagina on Jan. 26, 1939, and an estimated teacupful of pus escaped.

Examination on admission revealed a poorly nourished, elderly, white woman who did not appear ill. The oral temperature was 99.2° F. The weight was 89 pounds. The head systems were essentially normal. The thyroid was not palpable and the mouth was edentulous. Both breasts were atrophic. The heart and lungs were normal to auscultation and percussion. The blood pressure was 128 systolic



Fig. 1.—Biopsy from the cervix prior to treatment with stilbestrol. The mucosal surface shows no epithelial covering. ( $\times 100$ .)

and 76 diastolic and the pulse rate 68 per minute. There was a well-healed, mid-line, suprapubic scar, but no palpable abdominal masses or tenderness. The vulval skin was reddened and tender to manipulation, but showed no leucoplakia. Only one finger could be inserted into the vagina. Because of the constriction, the internal genitalia were not palpable. Rectal examination added nothing. Inspection through a small speculum showed the vaginal apex to be excoriated; the upper vagina was partially obliterated; the cervix could not be identified.

The urine contained no albumin, sugar, or abnormal microscopic elements. The hemoglobin was 12 Gm. (Haden-Hauser) with 4.35 million red blood cells and 9,150 white cells. Both the blood Wassermann and Kline reactions were negative. Cultures from the vagina revealed no gonococci, monilia, or trichomonads. Smears from the vagina were characteristic of the menopause with many leucocytes and only a few nucleated epithelial cells.

On March 13, 1939, under cyclopropane anesthesia biopsy of the vagina and cervix, and dilatation and curettage were done. Excoriated areas were noted over the entire vaginal mucosa. The vaginal biopsy was taken from one of these lesions. The uterine canal measured two inches in length. No curettings were obtained from the uterus. Grossly the tissue excised from the vagina was pinkish gray, slightly roughened on one aspect and somewhat hemorrhagic on the other. Microscopically there was a dense fibrous stroma with no covering epithelium. A few lymphocytes infiltrated the stroma. The cervical biopsy presented a pale,

3. In general, results were more or less comparable to those of natural estrogen, viz.: relief of menopausal syndrome, conversion of "menopausal" into "estrous" type of vaginal smear (Table IV), and restoration of the normal appearance of a previously atrophic vulva or vagina.

4. Like natural estrogen, stilbestrol acts on the Fallopian tubes, influencing peristalsis.

5. Treatment should continue until results appear, and should be resumed if relapses occur.

6. In 20 instances, the drug produced "vaginal bleeding." Patients should be warned about the possibility of pseudomenstrual bleeding on stopping treatment, and reassured as to its meaning.

7. The drug is active whether given hypodermically, by vaginal suppository, or by mouth. Average suppository dose is 0.1 mg., inserted twice a day. Average mouth dose is 1 mg. tablet each evening; the average hypodermic dose is 0.4 mg. three times a week.

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## HEMATOMETRA AND HEMATOCOLPOS FOLLOWING THE ADMINISTRATION OF STILBESTROL

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SUBSTITUTIONAL therapy with the female sex hormones is often followed by disappointing results and occasionally even with unusual reactions. The appearance of hematometra and hematocolpos in a woman who received large doses of stilbestrol for the treatment of severe senile vaginitis is reported.

A 54-year-old, married, white woman (Hospital No. 39-4426) was admitted to the University Hospitals on March 10, 1939, complaining of leucorrhea and vaginal spotting for ten years, and of soreness in the vagina for three years. Menstruation had appeared at the age of twelve years, occurred every thirty days, persisted for five days, and was painless. The menopause developed at the age of thirty-eight years, following extirpation of both tubes and part of one ovary. The indication for the operation was not known. Two full-term children were delivered in 1904 and 1906, respectively. No miscarriages were reported.

Shortly after the menopause a yellowish, slightly foul discharge appeared. The quantity of exudate increased gradually over the sixteen-year interval until a pad



formed. The uterus was slightly enlarged and the wall somewhat hemorrhagic. Both ovaries were atrophic. There were no pelvic adhesions. The Fallopian tubes had previously been excised.

The postoperative course was uncomplicated, and the patient was discharged on June 25, 1939. Late in July, 1939, it was reported that she was in good condition.

*Pathologic Report.*—The specimeus removed consisted of a uterus and two ovaries. The cervix was eroded and injected. The uterine cavity showed a polypoid mass, measuring 20 by 15 mm. The uterus was 7 cm. in length and the cervix was markedly dilated. The endometrium was granular and quite hemorrhagic. The myometrium was 20 mm. in thickness. The ovaries were small and atrophic.

Microscopically the cervical mucosa appeared normal. The stroma was infiltrated with lymphocytes, large mononuclear cells, many neutrophils, and red blood cells.

The endometrial glands (Fig. 2), which were lined by a single layer of low columnar epithelium, were somewhat tortuous and dilated, but were not hyperplastic or invasive. The myometrium was thick.

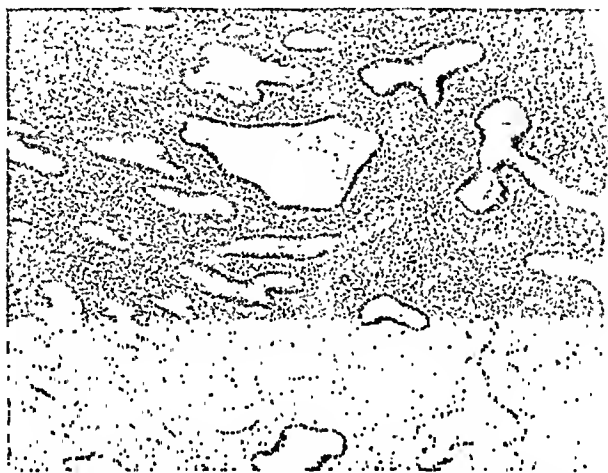


Fig. 2.—A section of the endometrium fourteen days after 290 mg. of stilbestrol given over a seventy-four-day interval had been discontinued. Notice the endometrial glands in the proliferative stage. The stroma is filled with red blood cells. ( $\times 100$ .)

The polyp was covered by a single layer of columnar epithelium. The stroma was rich in glands, and was infiltrated in areas with amorphous debris. Hemorrhages had occurred within the vascular stroma.

Both ovaries contained a few small simple cysts lined by columnar epithelium, and several corpora albicantia.

*Diagnosis:* Subacute cervicitis, endometrial polyp, and hematometra.

#### COMMENTS

Hyperplasia of the endometrium has been produced experimentally in rats (Burch, Williams, and Cunningham<sup>1</sup>), guinea pigs (Wolfe, Campbell, and Burch<sup>2</sup>), (Nelson<sup>3</sup>), mice (Parkes<sup>4</sup>), (Gardner, Allen, and Strong<sup>5</sup>), rabbits (Zondek<sup>6</sup>), and monkeys (Zuckerman and Morse<sup>7</sup>), by the administration of estrogenic hormone. Comparatively large doses given over relatively long periods were required before extensive endometrial hyperplasia occurred. In some instances growth of the endometrium in the proliferative phase may be associated with bleeding (Nelson<sup>3</sup> and Zondek<sup>6</sup>). Werner and Collier<sup>8</sup> were the first to produce uterine bleeding in castrated women by injection of estrogens. Since then, it has been demonstrated repeatedly that such bleeding may follow when the administration of ovarian hormone is discontinued (Engle, Smith, and Shelesnyak<sup>9</sup>), (Allen, Diddle, Burford, and Gardner<sup>10</sup>), and in a few cases, even after treatment has

pinkish gray color and was smooth. Histologically (Fig. 1) the fibromuscular tissue was partially hyalinized. There were no glands or epithelial covering.

The final diagnosis was nonspecific senile vaginitis. Five milligrams of stilbestrol was then prescribed as indicated in Table I. On April 28, 1939, the patient returned to the Clinic and reported marked symptomatic improvement. Both breasts had become somewhat tender and there had been frequent tingling. The vaginal soreness and burning had practically disappeared. The constricted outlet and the reddened vaginal mucosa were now pliable and soft. The uterus was small and freely movable, and the cervical mucosa was velvety in appearance. Vaginal smears contained numerous nucleated epithelial cells, but there were still many leucocytes. On the basis of the vaginal smears, the dosage of stilbestrol was continued.

From April 28 to May 30, the patient remained in excellent health. On May 31, pain was noted in the right lower abdominal quadrant on stooping. The medication was discontinued under the direction of the family physician, who subsequently discovered a tender mass in the lower abdomen. During the next twelve days the discomfort became progressively worse until medication was required for the pain. On June 12, 1939, she was readmitted to the Hospital. Physical examination disclosed a cystic mass arising from the pelvis to the right of the midline above Poupart's ligament. There was slight senile vaginitis. The cervix could not be seen or definitely felt. Both adnexa were free. In place of the uterus and protruding into the right pelvis and cul-de-sac was a grapefruit-sized, freely movable, cystic mass. Both parametria were clear and there was no tenderness. Smears from the vagina contained red blood cells, leucocytes, and many nucleated epithelial cells.

TABLE I. ORAL ADMINISTRATION OF STILBESTROL

DATE	DOSE	TOTAL DOSE	REMARKS
March 17 to March 30	5 mg. daily	70 mg.	
April 1 to April 9	5 mg. every other day	95 mg.	Tender breasts
April 13 to April 28	5 mg. every third day	125 mg.	Tingling in breasts
April 28, 1938			Vaginal smears contained many leucocytes
April 29 to May 31, 1939	5 mg. daily	290 mg.	
May 31, 1939			Pain in right side of abdomen
June 12, 1939			Vaginal smears contained red blood cells, leucocytes, and many nucleated epithelial cells
June 14, 1939			Hematometra. Total abdominal hysterectomy done

On June 14, 1939, under cyclopropane and ether anesthesia, vaginal examination was done. The vaginal mucosa was agglutinated below the cervix. The anterior vaginal wall just below the apex was bulging and a cystic mass the size of a three months' pregnancy could be felt bimanually. The vaginal protrusion represented the lower part of this cystic mass. On the basis of the clinical history and physical findings, and in view of the continued administration of large quantities of estrogenic hormone, a diagnosis of hematometra was made. By blunt dissection, beginning at the agglutinated fold in the upper vagina, the vaginal walls were readily separated and released approximately 200 c.c. of tarry viscid fluid. With the escape of the fluid, the abdominal mass entirely disappeared. The cervix could not be felt since it was so widely dilated; the examining finger could be passed to the uterine fundus. In order to minimize the risk of infection following this drainage and to make it safe for the patient to receive further female sex hormone for the senile vaginitis if necessary, abdominal total hysterectomy and bilateral oophorectomy were per-

## TREATMENT OF SENILE VULVOVAGINITIS WITH ESTROGENIC OINTMENT\*

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DEFINITE regressive changes of the ovaries take place following the menopause. There are concomitant and probably dependent trophic changes in the vagina and vulva. The development of these regressive morphologic changes is not surprising in view of the recognized growth function of the ovarian follicular hormones. These hormones are not only the principal determining factors in the development of the reproductive system, but at the period of menarche and during adult sexual life, they are indispensable for the maintenance of these tissues.

In a majority of menopausal patients, symptoms associated with these trophic changes do not appear. However, some individuals at this period exhibit clinical symptoms, of which pruritus, burning, especially upon urination, and dyspareunia are the most common. Associated systemic symptoms, such as hot flushes, mental irritability, depression, and in marked cases, suicidal tendencies, should be attributed to the general physiologic changes in the organism and as a part of the menopause, rather than to the local condition of senile vulvovaginitis.

The term, senile vulvovaginitis, appears to be as satisfactory as any generally applied to the condition. Adair<sup>1</sup> pointed out that kraurosis, leucoplakie vulvitis, and leucokraurosis, are commonly used interchangeably to describe the pathologic changes in the vulva. He suggested the use of the descriptive term "chronic atrophic dermatitis of the vulva." The gynecologic literature, as a rule, treats kraurosis vulvae, chronic senile vulvitis, leucoplakia vulvae, and senile vaginitis as separate clinical entities. It seems a more rational conception, however, to regard all of them as part of the same general degenerative process, due to the diminution and final withdrawal of the ovarian follicular hormone stimulus from the tissues of the uterus, vagina, and vulva. The local symptoms will vary and are dependent upon the anatomic site involved, and possibly upon the presence or absence of a rich peripheral nerve supply.

Previously, local treatment of senile vulvovaginitis with lotions, salves, etc., particularly for the relief of the severe pruritus, has been distinctly unsatisfactory. X-ray therapy has afforded but temporary relief in most cases, and more important, recurrences have been found to be refractory to further treatment. Injection of absolute alcohol has failed to give constant or permanent relief, and is attended with dangers of abscess formation and sloughing of the tissues.

\*Presented at the clinical meeting, Graduate Fortnight of the New York Academy of Medicine, October, 1939.

been prolonged for several weeks (Allen, Danforth, and Doisy<sup>11</sup>). Cystic and glandular hyperplasia in the human endometrium has also been reported by Kurzrok.<sup>12</sup>

Bleeding after substitutional therapy is similar to that which appears at the termination of an ovulatory cycle. Normal menstruation is apparently precipitated by the withdrawal or decrease of some stimulus necessary to maintain the endometrium in a hyperplastic state. Reports by other authors (Winterton and MacGregor<sup>13</sup>), (Kellar and Sutherland<sup>14</sup>), (Shorr and others<sup>15</sup>), indicate that withdrawal of stilbestrol produces bleeding similar to that induced by the cessation of ovarian hormone administration. Kellar and Sutherland are of the opinion that this is due to a local vascular phenomenon.

Our experience has confirmed the reactions reported after stilbestrol ingestion. Among 10 patients treated for senile vaginitis or menopausal symptoms for periods of five to seventy-four days, 3 had bleeding after the medication was stopped, 8 complained of nausea, and 4 had to discontinue therapy because of this reaction.

The end result in the case cited above cannot be satisfactorily explained. However, it would seem that, in the early stage of therapy, epidermization of the vagina was not sufficient to prevent obliteration of the vagina. It is interesting that administration of large doses of stilbestrol over a long period failed to bring about progressive changes in the smear picture. After endometrial proliferation had been stimulated, bleeding probably occurred in spite of the maintenance of the dosage. With the cessation of medication, the usual withdrawal bleeding was probably added. There seems to be a limit to the ability of the estrogenic stimulus to retain the endometrium without bleeding.

#### SUMMARY

Among 10 women given 1 to 5 mg. of stilbestrol daily, 3 had withdrawal bleeding and 8 had considerable and annoying nausea and vomiting.

Relatively large doses of stilbestrol were administered over a seventy-four-day period to a woman having senile vaginitis. The quantity given failed to bring about complete cornification of the vaginal mucosa, but did lead to uterine bleeding with the production of hematometra and hematocolpos subsequent to spontaneous obliteration of the vagina.

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Regular Allen-Doisy technique of assay was employed, and smears were taken daily at 11:00 A.M. and 3:00 P.M. The application was continued for four consecutive days. At the end of the third day, all vaginal smears were in full estrus, showing the usual field of cornified nonnucleated epithelial cells with no leucocytes.

It is interesting to note in these experiments that by inunction of the ointment, the entire group of rats (8) were brought into full estrus in the same time period; that is, the end of the second day, as would have been accomplished by injection of the estrogen.

Inasmuch as the rats reacted 100 per cent positive, it may be concluded that the quantity of estrogen in the ointment was in excess of the quantity required for the reaction.



Fig. 1.—Hypertrophic leucoplakic vulvitis. Note hypertrophy of the epithelium with parakeratosis. Hyaline zone underneath the hypertrophic basal layer of the epithelium.

#### CASE REPORTS

CASE 1.—L. D., aged 36 years, complained of burning and itching about the vagina, dyspareunia for a duration of two years. The patient had a salpingectomy and partial oophorectomy one year before onset of symptoms. Menses began at the age of 14, were fairly regular, lasting 6 days; but there had been a marked decrease in the amount of flow during the past two years. Upon examination, there was noted a thickened, dry skin about the vulva, with grayish white plaques in many areas. There were several fissures in the posterior commissure. The introitus was narrow. Vaginal examination was very painful. The cervix was moderately hypertrophied, but the corpus was small and fixed. Biopsy was taken at the vulvovaginal margin on May 14, 1938, and the following pathologic report was obtained. "The surface epithelium shows excessive cornification. The nuclei are preserved in the cornified cells. The individual epithelial pegs are irregular in shape, elongated, and enlarged due to hypertrophy of the basal layer. The corium reveals a marked infiltration with round cells and shows a broad hyaline zone underneath the basal layer of epithelium. There is fibrosis in the deeper portion of the corium. Diagnosis: Hyperkeratosis with hyalinization of the corium, and chronic inflammation" (Fig. 1). Estrogenic ointment was prescribed. A clinical note, made eight weeks later, stated the following: "The patient feels better, itching has disappeared, intercourse without pain.

Vulvectomy, the method of choice of Taussig,<sup>2</sup> is a major surgical procedure. It has the advantage, however, of eliminating the possible development of epithelioma, particularly the leucoplakic forms. At this time it should be stressed that any suspicious area be subject to biopsy examination before any type of therapy is instituted.

Recently, the estrogens have been used in the treatment of senile vulvovaginitis. This use of the estrogenic substances arose from the recognition of their specific growth influence upon the reproductive tract, including the external genitalia, and it was believed that therapeutic use might be made of these hormones in restoring the degenerating tissues to their normal state. In such treatment, it may be shown histologically that there is a restoration and re-establishment of normal growth processes and formation of new healthy tissues.

Early workers, J. A. Schockert,<sup>3</sup> W. Rust,<sup>4</sup> and C. B  cl  re,<sup>5</sup> made use of parenteral injections and reported good results. E. Clafften,<sup>6</sup> in 1937, was one of the first to report the use of an estrogenic ointment in severe cases of pruritus vulvae. He felt that the therapeutic effect of locally applied estrogens upon the affected tissues was greater than that produced by intramuscular injection of the same amount of hormone. This theory was corroborated by MacBryde,<sup>7</sup> who demonstrated the local action of estrogenic ointment upon the undeveloped female breast in a case of primary amenorrhea. The breast to which the estrogenic ointment was applied displayed marked growth, while the other breast, treated with the ointment base alone, failed to develop. This suggests that when active local stimulation is desired, the percutaneous administration is not only effective, but is, perhaps, to be preferred to the parenteral injection of the hormone.

A histologic study of the tissues involved in senile vulvovaginitis gives some evidence as to why topical application is more effective than hormone administered by injection. The vascular supply of the affected areas shows marked abnormalities, and it is possible that hormone carried through the circulation fails to reach the area, particularly the peripheral sites.

During the past two years, we have treated patients with senile vulvovaginitis with local application of estrogenic ointment with striking results. Estriol or trihydroxyestrin was chosen to be incorporated in the ointment base, inasmuch as it has been fairly well established that this particular estrogenic substance is more easily absorbed from the gastrointestinal tract than estrin or estradiol, consequently, we felt that it might be more easily absorbed percutaneously.

#### METHOD

The ointment base consists of 16 parts of cerate to 14 parts of castor oil. Each ounce contains 0.00752 Gm. of estriol. Estrogenic action of the ointment was determined by animal experiment, using ovariectomized white rats. These rats were taken from a group regularly used in routine assay of crystalline estrogenic compound by the Allen-Doisy technique. Vaginal smears were taken before the experiment and all animals were found to be in complete anestrus, with a field showing practically nothing but leucocytes.

The rats were shaved over a small area on each side of the middorsal line, just below the margin of the last rib. Applications of the ointment were made twice daily on these areas at 9:00 A.M. and 1:00 P.M. A total of 1 Gm. was distributed over both shaved areas.

epithelial zone. The deeper portions of the dermis show fibrosis. Diagnosis: Senile vulvovaginitis, atrophic form, with beginning ulceration" (Fig. 3). Estrogenic ointment was prescribed, and the patient reported marked improvement after two weeks. A month after therapy was instituted, all symptoms were relieved. The ulcerated areas had completely healed. Another biopsy



Fig. 3.—Atrophic vulvovaginitis, beginning ulceration. Note destruction of epithelium by inflammatory infiltration.



Fig. 4.—Complete restitution of squamous epithelium in atrophic vulvovaginitis. Note young vascular connective tissue in subepithelial zone.

was taken at that time. Pathologic report: "Squamous epithelium shows complete restitution. The inflammatory infiltration is replaced by young vascular connective tissue. Diagnosis: Complete restoration of vaginal epithelium" (Fig. 4). Treatment was continued for another month despite the patient being symptom free. Her condition remained satisfactory until three months later, when she reported a slight recurrence of symptoms. These were completely relieved by a two weeks' application of the ointment. Upon physical examination,

Upon examination, the vulva appears to be healthy. All fissures have healed, and no leucoplakic areas are present." At this time, another biopsy was taken, with the following pathologic report: "The hypertrophy of the surface epithelium is less pronounced. The process of cornification is normal. The individual pegs are more regular in shape. The corium shows a persistent hyaline zone, which is narrower than before. The chronic inflammation is still present. There is formation of young capillaries. Diagnosis: Chronic hypertrophic vulvitis in stage of healing." Treatment with estrogenic ointment was continued. Six weeks later, a third biopsy was taken. Pathologic report: "The surface epithelium shows scattered areas of hyperkeratosis. The basal layer of the epithelium does not show any hypertrophy. The stratification of the epithelium is normal. The corium is composed of young connective tissue with abundant capillaries.



Fig. 2.—Hypertrophic leucoplakic vulvitis after treatment with estrogenic ointment. Restoration to normal.

A few round cells are found in the deeper portions of the corium as remnants of the previous inflammation. Diagnosis: Tissue showing restoration to normal after chronic hypertrophic vulvitis" (Fig. 2). All treatment was discontinued, and the patient was free of symptoms until Sept. 16, 1939, when the burning and pruritus recurred. Examination revealed the reappearance of a few areas of leucoplakia. Estrogenic ointment was reapplied, and one month later, all symptoms and signs had disappeared.

CASE 2.—B. G., aged 70 years, complained of itching and burning about the vulva, especially disturbing at night. Patient said she felt as if she would "like to jump out of the window." Menses began at the age of 14, and were regular. Spontaneous menopause occurred seventeen years ago. There were six normal labors. Itching started one year ago, and has gradually increased in severity. Upon physical examination, the patient was an apprehensive elderly female in good general health. Locally, the vulva and vagina were quite inflamed, and showed marked atrophy with superficial ulceration in several areas. There was a slight cystocele and moderate rectocele. The uterus was atrophied. A biopsy was taken at the vulvovaginal margin on Feb. 11, 1939, and the pathologic report follows: "The squamous epithelium shows marked atrophy and beginning destruction by inflammatory infiltration, which is particularly dense in the sub-



2. Amelioration of symptoms occurs after a period of two to three weeks.

3. Systemic action by absorption of the hormone is evidenced by alleviation of such menopausal symptoms as hot flushes.

4. Recurrences may take place, but these respond promptly to further treatment with estrogenic ointment.

Acknowledgement is made to Dr. C. F. Longfellow, of G. W. Carnrick Co., of Newark, N. J., for supplying material used in this study.

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141 WEST 109TH STREET

## CESAREAN SECTION

### A COMPARATIVE STUDY

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THIS treatise was prepared with a fourfold purpose in view: *First*: To compare mortality and morbidity statistics on cesarean sections performed by obstetricians with those done by general surgeons. Each group claims that the operation is safer in its hands, but no statistics have been offered to prove the contention of either.

*Second*: To compare statistics on cesarean sections performed in a representative general hospital with those done in a representative maternity hospital. The assertion is frequently made that these operations belong only in the maternity hospital.

*Third*: To compare statistics from a general hospital between the years 1931 and 1939 with national statistics during the same period. For this purpose all available reports during these years have been compiled; these surveys comprise the work of thirty American authors and include 15,768 cesarean sections.

*Fourth*: To compare statistics on operations performed between 1931 and 1939 with those done before 1931. Since the report of Plass<sup>1</sup> in 1931, there has been no complete statistical survey of the literature on this subject. The report of Plass has been selected as the most complete survey previous to 1931.

Between Jan. 1, 1931 and March 1, 1939, there were 6,781 deliveries in St. Paul's Hospital; during this period there were 102 cesarean sections with an incidence of 1.50 per cent or one cesarean section to 66 deliveries by the vaginal route. These operations were performed by 37 different operators, 13 of whom were physicians with adequate obstetric training, whose practice is limited to obstetrics or obstetrics

the tissues appeared to be healthy. There has been no further therapy, and up to the present time, there has been no recurrence of symptoms.

CASE 3.—M. E., aged 48 years, complained of pruritus vulvae, onset nine months ago, followed by dyspareunia. The menopause occurred spontaneously five years ago. Previous treatment, with intramuscular injections of estrone, gave temporary relief of systemic symptoms. At this time, the patient still complained of arthritic pains, hot flushes, headaches, sweats, and of mental depression. Menses began at the age of 17, every twenty-nine days, duration three days. There were three normal deliveries 17, 16, 14 years ago. Physical examination: The patient appeared mentally depressed and emotionally unstable. Vaginal examination: The vulva was red and extremely inflamed. The skin was atrophied, with loss of normal folds, and showed superficial ulceration in many areas. The cervix and corpus were small. A biopsy was taken on June 18, 1938, and the pathologic report follows: "The surface epithelium is missing in many areas. Where present, it does not show hyper- or parakeratosis. The corium reveals marked edema and aggregations of round cells. Diagnosis: Atrophic vulvitis, ulcerative form." Estrogenic ointment was prescribed, and a clinical note, made four weeks later, states: "The itching is completely relieved for the first time since its onset." A second biopsy was taken on Aug. 10, 1938. Pathologic report: "The surface is covered with normal stratified squamous epithelium, showing the pegs to be somewhat flattened. The corium consists of young connective tissue with abundant distended capillaries. A few round cells are still found scattered throughout the newly formed connective tissue. Diagnosis: Restoration to normal of chronic vulvitis." A clinical note made at this time states: "All local and systemic symptoms improved." A follow-up examination on June 3, 1939, revealed no recurrence of symptoms.

#### DISCUSSION

Two clinical forms of senile vulvovaginitis are presented: the hypertrophic and atrophic types.

Both the hypertrophic and atrophic forms may be considered two different phases of the same condition. Adair and Davis<sup>1</sup> have pointed out that both forms may occur in the same patient and are part of the same disease entity. It seems likely that the initial stage is an inflammatory, hypertrophic condition, which, if it proceeds, develops into the atrophic stage. The pathogenesis seems definitely based upon an endocrine deficiency resulting from the retrograde changes in the ovary. In the hypertrophic form, the epithelium remains intact, and may show many areas of hyper- and parakeratosis, clinically described as leukoplakia. The corium reveals a hyaline zone with disappearance of elastic elements and inflammatory infiltration. The atrophic form is characterized by a loss of the surface epithelium, ulceration, and inflammatory infiltration with edema of the corium.

The pathogenesis of this condition is so little understood, that it is difficult to explain how both the hypertrophic and atrophic forms should be favorably influenced by the administration of the same hormone. Both, however, have been shown to react favorably to the percutaneous administration of estriol.

#### CONCLUSIONS

1. The use of estrogen (estriol) in an ointment base for local therapy in senile vulvovaginitis has proved of definite value.

laparotrachelotomy carries a better prognosis than the laparohysterotomy; Table II significantly substantiates this statement by the low cervical group carrying no mortality and only 9.8 per cent morbidity, while the classical group reveals a mortality rate of 4.0 per cent and a morbidity rate of 32.0 per cent.

There is a striking similarity between the statistics on indications in these two hospitals (Table III); one column represents 1,000 cesarean sections in a maternity hospital while the other represents 102 sections in a general hospital. The great difference between the two groups of contracted pelvis may be explained by the large foreign element in Chicago; contracted pelvis are fairly common in women of foreign extraction. This fact adequately explains the difference in repeat sections; a high incidence of contracted pelvis will carry a correspondingly high incidence of repeat sections. There is no explanation for the difference in incidence of hemorrhage and pathologic presentations as indications for section.

#### MATERNAL MORTALITY

There were two deaths following operation in this group of 102 cesarean sections; this gives a mortality rate of 1.96 per cent.

One death occurred in a 30-year-old primigravida who underwent a Porro cesarean section for abruptio placentae, after having been in labor for three hours with intact membranes. The patient had normal temperature, pulse rate, and respiratory rate during her entire postoperative period but died suddenly on the eighth day. Death was ascribed to pulmonary embolism; there was no autopsy.

The other death occurred in a 31-year-old septigravida who underwent a classical cesarean section for abruptio placentae after having been in labor for eight hours with intact membranes. The patient died seventeen hours postoperatively; the cause of death was given as pulmonary embolism; no autopsy was performed.

It is interesting that the only two deaths in this series should be surrounded by practically identical circumstances; both operations were performed by general surgeons; both were done for abruptio placentae; both were about the same age and both died because of pulmonary embolism.

#### MATERNAL MORBIDITY

The standard as advocated by the American Committee on Maternal Welfare was used in calculating the morbidity of these patients. Any patient with a temperature of 38.0° C. (100.4° F.) or over, recorded on any two days after the first twenty-four hours post partum, sublingual temperature readings having been made at least four times daily, is regarded as febrile.

There were 19, or 18.62 per cent, of the 102 patients who became febrile according to the above standard and 15, or 14.70 per cent, who remained in the hospital longer than fourteen days postoperatively. Of the 71 laparotrachelotomies done, 7, or 9.85 per cent, became febrile. Of the 25 laparohysterotomies, 8, or 32.0 per cent, became febrile. Four of the five laparohysterectomies became febrile, giving a morbidity of 80.0 per cent on this group. Of the 41 sections done by 24 general surgeons, 11, or 26.82 per cent, became morbid. Of the 61 sections done by 13 obstetricians, 8, or 13.11 per cent, became morbid.

#### INFLUENCE OF LABOR ON MORBIDITY

TABLE IV

	NUMBER	PER CENT OF TOTAL	NUMBER FEBRILE	PER CENT FEBRILE
Not in labor	52	51.0	6	11.5
In labor	50	49.0	13	26.0

Tables IV and V illustrate the well-established effect of prolonged labor on cesarean section morbidity. The morbidity rate on patients in labor was 2.2 times as great as that on patients not in labor. The morbidity rate on the group in labor twelve hours or more was 2.3 times as great as that on the group in labor less than twelve hours.

and gynecology; the remaining 24 operators may be classed as general surgeons with no special obstetric training.

TABLE I. COMPARATIVE STATISTICS

	OBSTETRICIANS		GENERAL SURGEONS		TOTALS AND AVERAGES	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Cesarean sections	61	59.80	41	40.20	102	100.0
Maternal mortality	0	0.0	2	4.87	2	1.96
Maternal morbidity	8	13.11	11	26.82	19	18.62
Fetal mortality	2	3.27	2	4.87	4	3.92

The most significant fact in Table I is that there have been no maternal deaths following cesarean sections performed by obstetricians since 1931. It is also significant that the morbidity rate of the group performed by general surgeons is twice as great as that of the obstetricians. From this table we find definite merit in the statement that the cesarean section is a safer operation in the hands of the obstetrician than in those of the general surgeon.

In analyzing Table II a reason is found for the fine record of the obstetricians; 76 per cent of the laparotrachelotomies were performed by them while they did only 16 per cent of the laparohysterotomies. Most authorities now agree that the

TABLE II. TYPES OF OPERATION

	LAPARO-TRACHELOT-OMY*	LAPARO-HYSTEROT-OMY**	LAPARO-HYSTEREC-TOMY†	RUPTURED UTERUS
Number	71	25	5	1
Total	69.7%	24.5%	4.9%	0.9%
Obstetricians	76.0%	16.0%	40.0%	100.0%
General surgeons	24.0%	84.0%	60.0%	0.0%
Mortality	0.0%	4.0%	20.0%	0.0%
Morbidity	9.8%	32.0%	80.0%	0.0%

\*Low cervical cesarean section.

\*\*Classical cesarean section.

†Porro cesarean section.

TABLE III. COMPARATIVE INDICATIONS

INDICATIONS	ST. PAUL'S HOSPITAL	CHICAGO LYING-IN HOSPITAL
Disproportion and dystocia	45.0	48.3
Contracted pelvis	13.7	33.3
Cephalopelvic disproportion	9.8	2.7
Prolonged labor with inertia	4.9	1.3
Cervical dystocia	4.9	2.1
Previous Dührssen's incisions	0.9	0.2
Uterine fibromyomas	1.9	1.3
Transverse, brow, or face presentations	8.8	0.7
Dystocia dystrophy syndrome	0.0	4.1
Hemorrhage	26.4	12.5
Abruptio placentae	5.8	4.6
Placenta previa	20.6	7.9
Toxemias and related conditions	12.7	12.3
Chronic nephritis	3.9	4.2
Pre-eclampsia (nonconvulsive)	8.8	6.5
Eclampsia	0.0	0.9
Essential hypertension	0.0	0.7
Previous cesarean section	12.7	27.9
Recent laparotomy	0.9	0.0
Ruptured uterus	1.9	0.0

TABLE VIII. NATIONAL STATISTICS 1931-1939

AUTHOR	YEAR	NUMBER DELIV- ERIES	NUMBER SECTIONS	PER CENT SECTIONS	PER CENT MAT. MORT.*	PER CENT MAT. MORBID.**	PER CENT FET. MORT.***
Johnston and Smith <sup>3</sup>	1931	3,632	107	2.77	14.4	---	12.14
Adams <sup>4</sup>	1932	19,313	217	1.12	4.6	35.4	10.1
Skeel and Jordan <sup>5</sup>	1932	92,117	1,047	2.2	7.15	---	---
Sackett <sup>6</sup>	1932	18,446	578	3.14	4.32	---	---
Seeley <sup>7</sup>	1932	33,988	203	0.59	4.43	---	12.8
Courtiss and Fisher <sup>8</sup>	1932	31,613	1,000	3.1	5.9	64.0	---
Lull <sup>9</sup>	1933	35,284	573	1.6	6.8	---	12.8
Daichman and Pomerance <sup>10</sup>	1933	29,178	733	2.5	3.4	46.8	6.5
Colvin <sup>11</sup>	1933	20,286	220	1.08	5.5	39.5	16.4
Smith <sup>12</sup>	1933	98,108	1,556	1.5	4.9	---	---
O'Connor <sup>13</sup>	1934	13,154	436	3.3	4.6	33.5	9.5
Palmer <sup>14</sup>	1934	6,533	157	2.4	4.5	---	9.9
Stein and Leventhal <sup>15</sup>	1935	15,136	381	2.52	2.36	36.48	4.93
Stander <sup>16</sup>	1935	5,456	153	2.8	0.65	---	7.1
Waters and Leavitt <sup>17</sup>	1935	8,852	177	2.0	3.9	12.4	11.8
Siegal and Savage <sup>18</sup>	1935	14,504	518	2.8	7.35	66.0	15.1
Schwarz and Paddock <sup>19</sup>	1936	13,577	218	1.6	4.1	---	5.9
Feiner <sup>20</sup>	1936	23,031	347	1.56	3.74	22.9	2.01
Duncan and Doyle <sup>21</sup>	1937	22,880	703	3.07	4.3	---	---
Gustafson <sup>22</sup>	1937	7,368	366	4.8	6.8	22.1	4.8
Schulze <sup>23</sup>	1937	12,246	38	0.31	5.5	---	6.25
Reddock and Howell <sup>24</sup>	1937	39,480	329	1.2	8.04	75.2	17.0
Reekie and Kimball <sup>25</sup>	1937	3,476	158	2.2	5.06	17.8	12.6
Campbell <sup>26</sup>	1937	4,979	482	9.68	0.826	---	3.51
De Normandie <sup>27</sup>	1938	62,228	2,106	3.3	3.1	---	9.2
King and others <sup>28</sup>	1938	92,936	1,108	1.2	5.9	65.7	10.8
Soule <sup>29</sup>	1938	17,170	340	1.9	2.96	---	8.6
Daichman and Pomerance <sup>30</sup>	1939	11,210	380	3.3	2.1	46.8	5.5
Daily <sup>2</sup>	1939	18,009	1,000	5.5	0.8	43.8	4.3
Schumann <sup>31</sup>	1939	8,528	137	1.6	2.91	6.0	2.5
Totals		782,718	15,768	2.55†	4.69†	37.29‡	8.88§

\*Maternal mortality.

\*\*Maternal morbidity.

\*\*\*Fetal mortality.

†Based on 30 reports.

‡Based on 17 reports.

§Based on 25 reports.

TABLE IX. COMPARATIVE STATISTICS

NAME OF REPORT	NUMBER DELIVERIES	NUMBER SECTIONS	PER CENT SECTIONS	PER CENT MAT. MORT.	PER CENT MAT. MORBID.	PER CENT FET. MORT.
National before 1931*	262,852	2,289	0.77	9.45	----	11.92
National 1931-1939**	782,718	15,768	2.55	4.69	37.29	8.88
General Hospital 1931-1939†	6,781	102	1.50	1.96	18.62	3.92
Maternity Hos- pital 1931-1939‡	18,009	1,000	5.50	0.80	43.80	4.30

\*Based on report of Plass.<sup>1</sup>

\*\*Based on report of 30 authors.

†Based on St. Paul's Hospital report.

‡Based on Chicago Lying-in report—Daily.<sup>2</sup>

TABLE V. EFFECT OF TIME ELEMENT ON MORBIDITY

	NUMBER	PER CENT OF TOTAL IN LABOR	NUMBER FEBRILE	PER CENT FEBRILE
In labor less than 12 hours	15	30.0	2	13.3
In labor 12 hours or more	35	70.0	11	31.4

## INFLUENCE OF RUPTURED MEMBRANES ON MORBIDITY

TABLE VI

	NUMBER	PER CENT OF TOTAL	NUMBER FEBRILE	PER CENT FEBRILE
Membranes intact	91	89.3	12	13.1
Membranes ruptured	11	10.7	7	63.6

TABLE VII

	NUMBER	PER CENT OF TOTAL	NUMBER FEBRILE	PER CENT FEBRILE
Ruptured less than 12 hours	5	45.4	3	60.0
Ruptured 12 hours or more	6	54.6	4	66.6

Tables VI and VII illustrate the marked increase in risk when cesarean section is performed on a patient with ruptured membranes. The morbidity rate on patients with ruptured membranes was 4.8 times as great as the rate on patients whose membranes were intact at the time of operation. These figures indicate that the morbidity rate increases markedly when the membranes rupture, but the rate does not change materially after the time of rupture. This statement is substantiated by Daily<sup>2</sup> who found only 5.0 per cent difference in morbidity between the two twelve-hour periods; his report consisted of 1,000 cesarean sections.

## FETAL MORTALITY

Six, or 5.88 per cent, of the infants were stillborn; these cases all occurred following abruptio placentae and may be classed as inevitable.

Four, or 3.92 per cent, died in the neonatal period. One death occurred in a 4,100 Gm. postmature infant, following a thirty-two-hour labor; death occurred one hour post partum. The other three infants were premature; each weighed less than 2,500 Gm. The latter three cases all followed placenta previa. Two neonatal deaths were on the obstetrical service and 2 were on the general service.

## PREVIOUS CESAREAN SECTIONS

Nineteen, or 18.0 per cent, of these patients had one or more previous cesarean sections. In 13 instances (12.7 per cent), previous section was the only indication for operation. Sixteen, or 15.6 per cent, had only one previous section; 3, or 2.9 per cent, had two previous sections. None had more than two.

## PREVIOUS STILLBIRTHS

Of the 43 women who had previously borne children, 11, or 25.5 per cent of these, had experienced previous stillbirths. Most of these stillbirths had been caused by prolonged labors or difficult instrumental deliveries. The indication for cesarean section in 8 of these cases was contracted pelvis; the other 3 were performed only because of the history of previous difficult deliveries with resultant stillbirths.

# THE ASSAY OF POSTERIOR PITUITARY EXTRACT (PITOCIN) UPON THE PREGNANT HUMAN UTERUS WITH THE LORAND TOCOGRAPH\*

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## INTRODUCTION

NUMEROUS procedures have been employed for recording the movements of the pregnant, human uterus, and for measuring its contractile response to the administration of drugs. The most frequently used methods for registering uterine activity are the following: (a) Measurement of the contractions of strips of isolated muscle suspended in oxygenated Ringer's solution; (b) measurement of the changes in intrauterine pressure which are registered by a balloon placed within the pregnant, or immediately post-partum, uterus; (c) measurement of the changes in the contour of the abdominal wall, and therefore, indirectly, of the contour of the pregnant uterus, which occur with each uterine contraction.

In the case of the muscle strip preparation, its most obvious disadvantage is that it is isolated from both its nerve and hormonal connections. The uterine balloon also has disadvantages, i. e., the danger of puerperal sepsis and the fact that the balloon, acting as a foreign body, tends to irritate the uterus.

The method of studying the uterine contractions through the medium of the abdominal wall eliminates certain of the disadvantages of the other methods, but the majority of the devices which have been devised for this purpose, have been so complicated, either in construction or in operation, that they have had limited clinical value. Due to the disadvantages of all previous methods, little progress has been made at the bedside in studying the motility of the pregnant, human uterus.

Recently, Lorand<sup>1</sup> has developed a simple and efficient apparatus (tocograph) for recording the movements of the pregnant, human uterus through the medium of the abdominal wall. Experience with it in studying the uterine contractions which occur under a variety of conditions confirms the above statement. The present report deals solely with its employment in measuring the response of the pregnant, human uterus to extract of the posterior lobe of the pituitary gland, and is being made for two reasons: To indicate the value of the tocograph as an instrument for studying the effect of pituitary extract upon the pregnant uterus, and to show how its use can be of assistance to the obstetrician at the bedside.

\*Read at a meeting of the New York Obstetrical Society, December 12, 1939.

## CONCLUSIONS

The comparisons previously proposed have been made with the following results:

1. Comparative statistics prove that cesarean section is twice as safe in the hands of the obstetrician, in comparison with the general surgeon.

2. The cesarean section is safer in a maternity hospital than in a general institution; this verdict is reached despite the fact that both the maternal morbidity and fetal mortality rates were lower in the general hospital reported. Results were based on the mortality rate of the general hospital being 2.4 times as great as the rate in the maternity hospital.

3. Statistics from St. Paul's Hospital between the years 1931 and 1939 compare very favorably with national averages for the same period. The national maternal mortality rate was 2.3 times greater than that of the general hospital; the national maternal morbidity rate was 2.0 times greater and the national fetal mortality rate was 2.2 times greater.

4. Comparative statistics demonstrate that the incidence of cesarean section is 3.3 times greater since 1931 than it was before that year. Despite the fact that it is resorted to more frequently it has become a much safer operation than it was formerly. Before 1931 the maternal mortality rate was 2.0 times greater than it has been since that year; the fetal mortality rate was 1.3 times greater in the former period.

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of approximately 150 Gm. to displace it, operates a writing point which moves at right angles to a strip of millimeter, cross section paper, which in turn is moved by a clockwork at the rate of 1 mm. in twelve seconds. The excursion of the writing pen is seven times greater than that of the rod in contact with the abdomen.

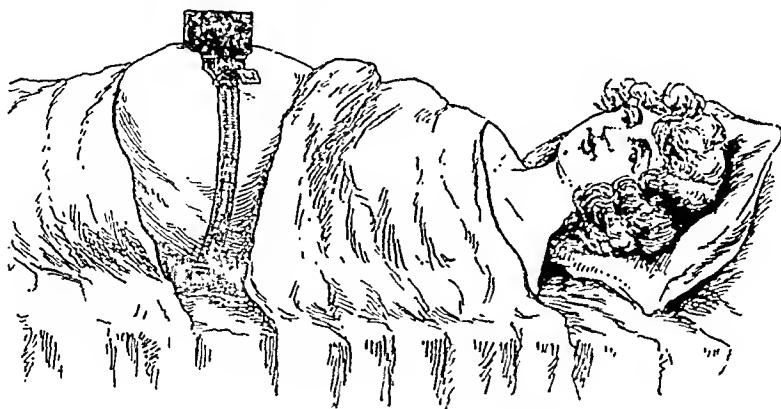


Fig. 3.—Lorand tocograph strapped to abdomen with an elastic belt in position for recording.

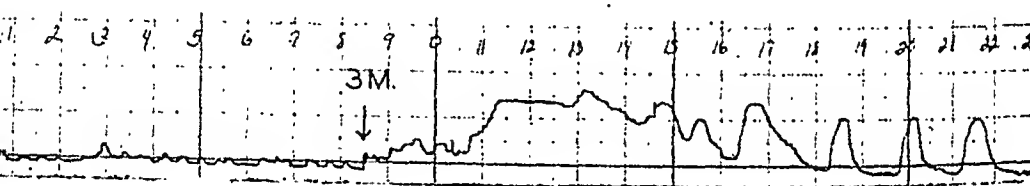


Fig. 4.—Tocographic record of uterine activity of Patient M. L. made at 10:21 A.M., ten days before labor. Numbers across top of record indicate intervals of two minutes. Three minims (M) of pitocin given hypodermically at arrow. Note tetanic contraction preceding rhythmic waves.

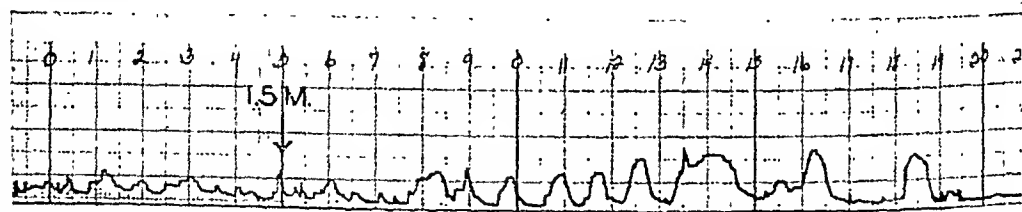


Fig. 5.—Patient M. L. Tracing started at 11:27 A.M. At arrow 1.5 min. of pitocin given hypodermically. Note absence of tetanus.

The tocograph will record changes in the contour of the abdominal wall which are induced by sneezing, coughing, vomiting, laughing, fetal movements, and uterine contractions, but does not register those which result from maternal respiration, intestinal action, or the pulsations of the aorta. With the patient resting quietly upon her back, uterine contractions and fetal activity are the only movements recorded.

The sensitivity of the device is indicated by the fact that an excursion of the writing point of  $\frac{1}{2}$  mm. is easily read. This represents a movement of the anterior abdominal wall of one-seventh of that magnitude.

### RESULTS

The uterine movements which take place during the last two months of pregnancy, and during labor, have been recorded for more than 300 patients, of which number, 15 have been treated simultaneously with hypodermic injections of solution

## MATERIALS AND METHODS

*The Lorand Tocograph.*—The tocograph (Figs. 1 and 2) consists of a set of levers enclosed in a metal box, 9.5 by 11 cm. square, by 6 cm. high. The box is fastened to the anterior abdominal wall with an elastic belt (Fig. 3). The alteration in the contour of the abdominal wall, which takes place with each uterine contraction, displaces into the tocograph a metal rod 6 mm. in diameter, which, when at rest, projects 5 mm. from the bottom of the box. The rod, requiring a force

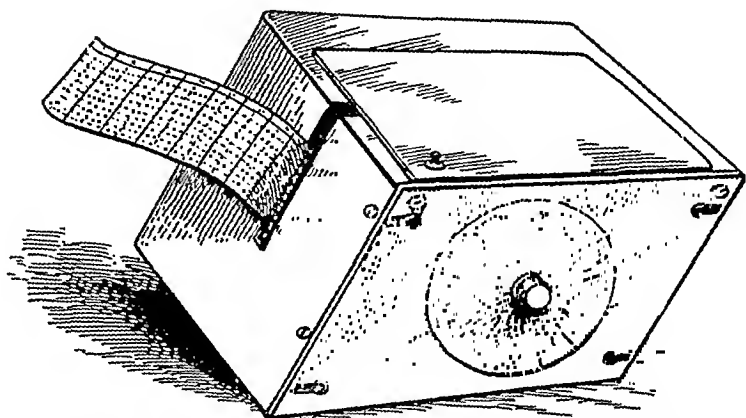


Fig. 1.—Exterior view of Lorand tocograph. Bottom of apparatus turned up to disclose end of movable rod which makes contact with anterior abdominal wall of patient.

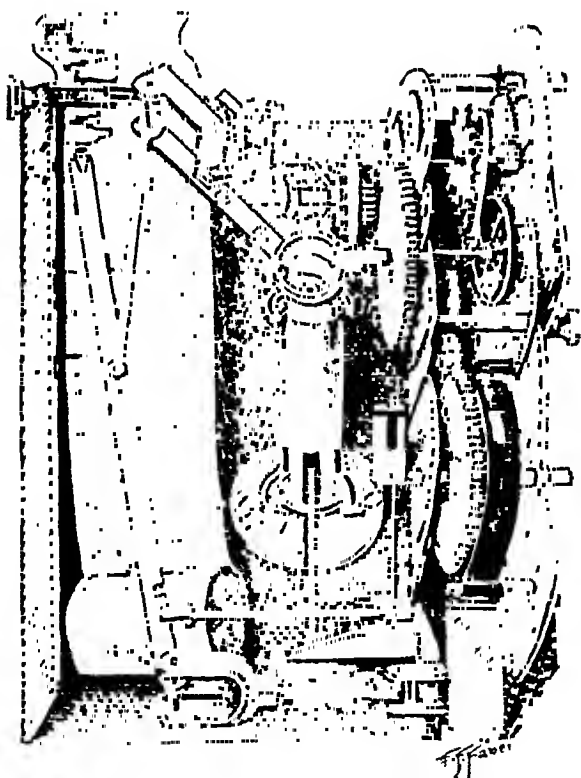


Fig. 2.—Interior view of Lorand tocograph. Showing lever arrangement, paper strip for permanent record of uterine contractions, and clockwork mechanism. Conical-shaped inkwell on end of recording lever moves at right angles to length of paper strip. The paper is drawn forward by the clockwork at the rate of 1 mm. in twelve seconds.

of the posterior lobe of the pituitary gland, in most cases pitocin (Parke, Davis & Co.). The value of the tocograph as an instrument for recording the response of the uterus to this substance is well exemplified by the accompanying tracings of Patient M. L.

The tracings reproduced in Figs. 4 to 7, inclusive, were made on the tenth day before the onset of labor. The tracing in Fig. 8 was made during labor. The latter tracing is shown in order to indicate the type of uterine activity which occurs under normal conditions, and which, consequently, is the type of activity which should be reproduced by an oxytocic agent.

The first part of the tracing in Fig. 4 (reading from left to right) shows the type of uterine movements occurring under normal conditions. At the arrow the patient received 3 minims of pitocin. This produced a tetanic contraction before rhythmic waves became established. Evidently this dose was too large to bring about at once, the rhythmic type of activity which occurred later, and which is to be observed at the time of labor (Fig. 8).

Fig. 5 shows the type of uterine activity one hour later than that recorded in Fig. 4, and the effect of only 1.5 minims of pitocin. This smaller dose failed to cause a tetanic contraction.

The tracing in Fig. 6 was made two hours after that reproduced in Fig. 5. Here two minims of pitocin again produced a spasm which lasted at least twelve minutes. This record was stopped before rhythmic contractions were inaugurated.

Fig. 7 shows the effect of 1 minim of pitocin given twice. Four doses of this size failed to produce tetanic activity.

#### DISCUSSION

Properly used, the oxytocic drugs should form one of the most important aids to obstetric practice. Their improper use on the other hand has resulted many times in serious consequences to either mother or child or both. These unfortunate results have been due in most cases, either to improper indications for administration, or because of excessive dosage. One reason for the use of inappropriate amounts of the oxytocic drugs has been our lack of knowledge regarding the size of the dose which will produce optimum results. Ignorance in this matter has been due, in part at least, to the fact that we have lacked a suitable method for measuring the effectiveness of various drugs upon the pregnant, human uterus.

The Lorand tocograph appears to be a very useful instrument for studying uterine motility at the bedside, and from our experience is an excellent device for measuring the effect of oxytocic drugs upon the pregnant, human uterus. The apparatus is small, compact, easy to use, and gives no discomfort to the patient. It registers minute changes in uterine activity, and gives a clear-cut record which is easy to read. The minuteness of the changes in uterine activity which it registers, makes it an excellent instrument for measuring the effects of very small differences in the amounts of oxytocic drugs which are given to the patient. It is for this reason that it should be a useful instrument to the clinical pharmacologist.

The tocograph should be an equally useful instrument for the obstetrician. It permits him, first of all, to determine the characteristics of the normal uterine activity, which occur at the time of labor. It will tell him the nature of the uterine activity which is going on at the time that he wishes to administer an oxytocic drug. It will inform him as to whether a given dose of the drug is being effective, and just how soon that effect begins. It will register the fact that a given dose of an

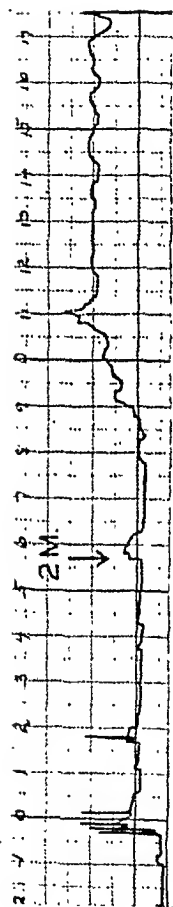


Fig. 6.—Patient M. L. Tracing started at 1:45 P.M. Two minims of pitocin given at arrow. Note long tetanic contraction.

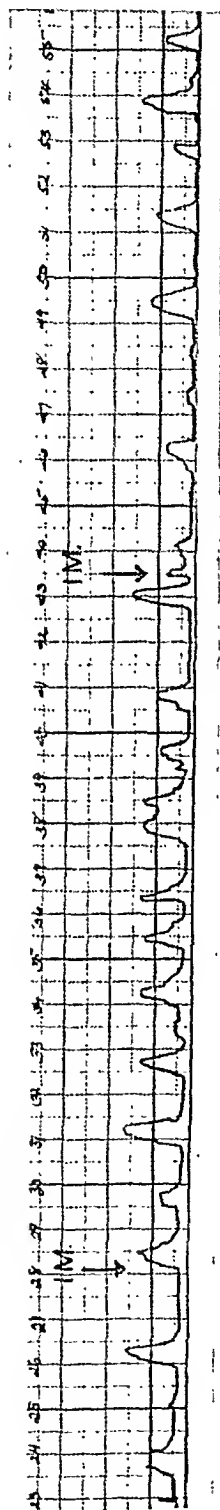


Fig. 7.—Patient M. L. Tracing started at 3:06 P.M. One minim of pitocin given at arrows. Note absence of tetanus.

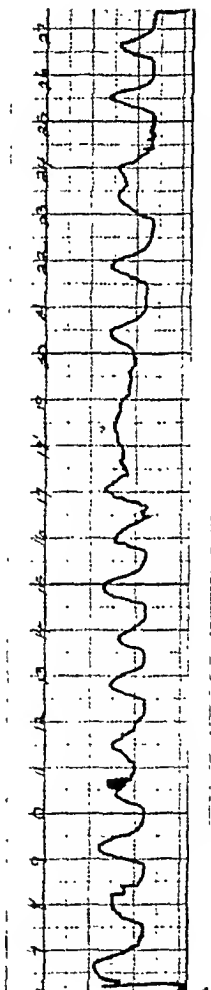


Fig. 8.—Patient M. L. Tracing made during first stage of labor. Note rhythmic nature of waves.

## PREGNANCY AND HEART DISEASE

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ALTHOUGH the care of the pregnant patient with heart disease is an individual problem, there are certain general factors common to most cases. Jensen<sup>1</sup> recently compiled the available literature on the subject and pointed to the fact that comparatively little is known of the life histories of cardiac patients, thus making controls difficult to obtain.

In this study, therefore, I wish to present the life cardiac histories of 49 patients who were pregnant a total of 244 times, and then compare them with a group of 41 nulliparous women who had almost identical heart lesions. Both groups of patients were similar in all respects except that one consisted of the gravid and the other of nongravid women. They were of the same social and economic status, had lived in or about Chicago since birth, and had reached the childbearing age before cardiac symptoms, failure, or auricular fibrillation appeared. These patients were seen and followed during a period of nine years, and all information was obtained directly from them. Any reasons as to why the 41 nongravid women with heart disease did not or could not become pregnant were omitted, because this had no bearing on the problem under consideration and no relation to the heart disease.

The number of pregnancies among the 49 parous women varied from 1 to 22, and approximately one-half (49.2 per cent) had 1 to 3 children. Three-fourths of them had less than 5 children (Table I). All of the 49 patients were compensated before the first pregnancy occurred, and none went into the first labor while decompensated or fibrillating. For comparative purposes it is important to bear this fact in mind, though they were not selected cases. With one exception all of the patients married and became pregnant for the first time before the age of 25 years (Table II). And all, except 4 (8.1 per cent), had the last pregnancy before the age of 35.

TABLE I. NUMBER OF PREGNANCIES IN 49 CASES

PREGNANCIES	NO. OF CASES	PER CENT	PREGNANCIES	NO. OF CASES	PER CENT
1	9	18.4	9	3	6.1
2	10	20.5	10	2	4.0
3	5	10.3	12	3	6.1
4	8	16.4	13	1	2.0
5	4	8.2	16	1	2.0
6	1	2.0	22	1	2.0
8	1	2.0	Average—4.9 pregnancies		

The cardiac lesions in the parous and in the nonparous women were almost similar, as 96 per cent of the former had mitral stenosis, alone or in combination

oxytocic drug is producing a desired type of uterine activity, or one which is not satisfactory. It will furthermore tell the obstetrician when a given dose is becoming ineffective, so that another can be given without undue delay.

#### SUMMARY AND CONCLUSIONS

1. The Lorand tocograph, for recording the movements of the uterus late in pregnancy and during labor, is described.

2. Typical records of the uterine response, late in pregnancy, to varying sized doses of posterior pituitary extract given hypodermically are reproduced.

3. From experience gained with the tocograph in studying the contractile reaction of the uterus to the hypodermic administration of posterior pituitary extract, it is concluded: (a) that the tocograph is a useful instrument for measuring the effect of pituitary extract upon uterine motility, and (b) that it should be a valuable adjunct to the armamentarium of the obstetrician when administering an oxytocic drug to a pregnant patient.

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#### DISCUSSION

DR. SAMUEL R. M. REYNOLDS.—Among many interesting points, Dr. Murphy has said there is an accelerating development of a characteristic pattern of uterine motility preceding the onset of labor. He points out that the tension of the uterine wall increases during the last week of pregnancy.

Recent studies in animals have established that shortly before the onset of labor there are varying degrees of tension on different parts of the uterine wall. With increasing distention near term this tension increases very considerably, and it becomes uniform over the entire surface of the uterus. This appears to be an essential physical condition for labor.

The background of this pattern of uterine motility stems from the tension-change in the uterine wall, and this, in turn, is attributable to the following two facts: First, as term approaches, free estrogen circulates and this sets up metabolic conditions in the myometrium, favoring increased uterine activity and irritability; second, in the latter part of gestation, the uterus stops growing as the products of conception increase in size at a rapid rate. These conditions, increased irritability of the myometrium and limited uterine growth with increased distention, provide the background for cervical dilatation, orientation of the fetus, and a typical pre-labor pattern of uterine contractility. Against such a background, I believe, the inertia-type of motility must be explained. The studies in which Dr. Murphy is engaged may prove most useful in elucidation of the physiologic deficiencies in those cases of uterine inertia not complicated by mechanical faults.

age. Between the ages of 26 and 35 years, when approximately half (49 per cent) of the parous women were through their last pregnancy, 20 (40.9 per cent) had the onset of cardiac failure, which compares with the onset in 19 (46.6 per cent) of the 41 nongravid women (Table V).

The ages at death were almost similar in both groups as 22 (44.8 per cent) of the parous women died during the important childbearing age of 16 to 35 years as compared with 17 (41.3 per cent) of the nonparous who expired during the same age period (Table V).

TABLE V. PER CENT OF THE AGE GROUPS AT RECOGNITION OF CARDIAC LESION, AT ONSET OF CARDIAC FAILURE, AND AT DEATH

AGE GROUPS	RECOGNITION OF LESION				ONSET OF FAILURE				AGES AT DEATH			
	PAROUS		NON-PAROUS		PAROUS		NON-PAROUS		PAROUS		NON-PAROUS	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
6-10	4	8.2	2	4.8	-	-	-	-	-	-	-	-
11-15	9	18.4	8	19.7	-	-	-	-	-	-	-	-
16-20	23	46.9	11	26.9	3	6.1	7	17.0	-	-	2	4.8
21-25	10	20.5	9	21.9	7	14.3	2	4.8	5	10.2	7	17.1
26-30	1	2.0	7	17.0	11	22.5	8	19.7	5	10.2	4	9.7
31-35	2	4.0	3	7.3	9	18.4	11	26.9	12	24.4	4	9.7
36-40	-	-	1	2.4	14	28.6	7	17.0	9	18.4	8	19.7
41-45	-	-	-	-	3	6.1	3	7.3	8	16.4	9	21.9
46-51	-	-	-	-	2	4.0	3	7.3	10	20.4	7	17.1
Totals	49	100.0	41	100.0	49	100.0	41	100.0	49	100.0	41	100.0

#### COMMENT

Much has been said concerning the care of the patient with heart disease during pregnancy and labor. It is a highly individualized problem, but other factors, considered in this report, have not been analyzed in full previously.

Daly<sup>2</sup> emphasized that nearly every woman with organic heart disease, regardless of the lesion, can carry through pregnancy successfully. It is best that the patient be fully compensated at the time the pregnancy is undertaken. Reid<sup>3</sup> stated that married women with rheumatic heart disease die before their time because of the natural evolution of this disease rather than because of the childbearing. The present study confirms his statement. Jensen<sup>4</sup> pointed out that the evil effect of pregnancy on heart disease seems chiefly to be that it may precipitate congestive failure when it is imminent and aggravate it when it is present. The soundest advice available on the subject today is that offered by Levine,<sup>5</sup> who, among other valuable points, stated, "Realizing that there is always a slightly greater risk among pregnant organic cardiaes than among normal women, no matter how apparently trivial the disease may be, I feel that if there are already three children, under no circumstances should any more pregnancies be undertaken."

From this analysis I wish to suggest that women with compensated rheumatic heart disease be advised to marry early, 18 to 21 being the optimum age, and to bear their children before the age of 25 if they desire a minimum of risk. This statement is made not because pregnancy shortens the length of life in the cardiac patient, but because of the course of the heart disease. Early marriage and early childbearing not only have a minimum risk, but they also provide a longer period in which to raise the children. Only three (6.1 per cent) of the 49 parous women became decompensated before the age of 20, and none died before

TABLE II. PER CENT OF AGE GROUPS AT THE FIRST AND THE FINAL PREGNANCY

AGES	FIRST PREGNANCY		FINAL PREGNANCY	
	NO.	PER CENT	NO.	PER CENT
16-20	33	67.3	7	14.3
21-25	15	30.7	14	28.6
26-30	—	—	14	28.6
31-35	1	2.0	10	20.4
36-40	—	—	4	8.1
Totals	49	100.0	49	100.0

with an aortic lesion, while 95.2 per cent of the latter group had the same valvular deformities (Table III).

The known duration of the heart lesions varied from one to thirty-eight years in both groups (Table IV). The duration of the disease from the onset of rheumatic fever was not accepted as a criterion of the total duration, since less than half of the patients gave a history of joint manifestations. Then again, a small number of patients in both groups gave a history of rheumatic fever after the cardiac lesion had been recognized. In 32 (65.3 per cent) of the 49 parous women, the cardiac lesion was known to be of less than twenty years' duration, as compared with 35 (79.8 per cent) of the 41 nonparous women. It was known to be of longer duration, twenty-one to thirty-eight years, among 17 (34.7 per cent) of the parous and in 8 (20.2 per cent) of the nonparous women. As a rule the cardiac lesions were recognized earlier in the gravid women, mainly because of the pregnancies. In 73.5 per cent of the parous and in 51.4 per cent of the nulliparous the heart lesions were recognized before the age of 20 (Table V). This, in spite of the fact that in 13 parous women the cardiac condition was not recognized until after one or more pregnancies.

Although 98 per cent of the gravid patients had completed their first pregnancy before the age of 25, the onset of cardiac failure occurred before this age in only 10 (20.4 per cent) of the 49 patients. This figure compares with the nonparous group, in 9 (21.8 per cent) of whom cardiac failure appeared before the same

TABLE III. HEART LESIONS

LESION	PAROUS		NONPAROUS	
	NO.	PER CENT	NO.	PER CENT
Mitral stenosis	41	83.6	36	88.0
Mitral and aortic insufficiency and stenosis	6	12.4	2	4.8
Mitral stenosis and tricuspid insufficiency	1	2.0	2	4.8
Mitral stenosis, aortic insufficiency, and tricuspid stenosis	—	0.0	1	2.4
Pulmonary stenosis	1	2.0	0	0.0
Totals	49	100.0	41	100.0

TABLE IV. KNOWN DURATION OF THE HEART LESIONS

DURATION YEARS	PAROUS		NONPAROUS	
	NO.	PER CENT	NO.	PER CENT
1-5	2	4.0	—	—
6-10	5	10.2	7	17.0
11-15	11	22.5	12	29.0
16-20	14	28.6	14	33.8
21-25	6	12.2	5	13.0
26-30	8	16.4	2	4.8
31-38	3	6.1	1	2.4
Totals	49	100.0	41	100.0



# VITAMIN B<sub>1</sub> DEFICIENCY AS AN ETIOLOGIC FACTOR IN PREGNANCY TOXEMIAS

## PART II

A. C. SIDDALL, M.D., OBERLIN, O.

**I**N A preliminary report<sup>1</sup> the hypothesis was advanced that an inadequate intake of vitamin B<sub>1</sub> may cause altered function of the pituitary gland, thus giving rise to the toxemias of pregnancy. This present, second report gives the results of vitamin B<sub>1</sub> injections in patients with pre-eclampsia and comments are added on the geographic distribution of vitamin B complex deficiencies in relation to the distribution of eclampsia.

In order to try the curative effect of vitamin B<sub>1</sub> in a reasonable number of patients with pre-eclampsia, it was necessary to seek material.\* A total of 20 cases of pre-eclampsia have now been studied. Most of these patients were given 6.7 mg. of thiamin chloride† intramuscularly once daily for ten days. Observations were made regarding blood pressure, edema, urine, and subjective symptoms. The results show without exception that there was no more improvement in these patients thus treated than seen in untreated patients with only bed rest. Therefore I believe that vitamin B<sub>1</sub> as given in this experiment has no curative value in the treatment of pre-eclampsia. Strauss<sup>2</sup> has reported that he obtained no evidence that a deficiency of vitamin B<sub>1</sub> plays a role in the water retention in pregnancy toxemias. Whether vitamin B<sub>1</sub> is of value as a prophylactic measure in the prevention of the pregnancy toxemias, remains to be seen after extended trial in prenatal clinics. McIlroy<sup>3</sup> emphasizes the nutritional aspect of toxemia when she says, "From clinical experience I am firmly convinced that the way of research and progress lies, not so much in a more or less lengthy search for illusive toxins, as in the investigation of toxemia as a deficiency disease."

*Comment.*—The geographic distribution of eclampsia shows a striking relationship to the distribution of the vitamin B complex deficiencies. In some parts of the world it is predominately nicotinic acid deficiency as shown by the high incidence of pellagra while in other parts of the world the deficiency is thiamin chloride as shown by the prevalence of beriberi. For the United States of America this correlation between vitamin B complex deficiencies and eclampsia is shown in Fig. 1.<sup>4</sup>

In this map it is shown that eclampsia is prevalent more markedly in the southeastern quadrant of the United States. It is a significant fact that in this same quadrant occurs almost all the pellagra<sup>5</sup> in the States. It has been estimated that some 200,000 persons<sup>6</sup> are afflicted with pellagra in this area. The highest incidence is among adult married women which suggests a relationship between pellagra and pregnancy

\*I am indebted for the kind cooperation of Drs. Paul Titus, Philip F. Williams, Clifford B. Lull, D. S. Hillis, and Sidney Stone.

†The thiamin chloride used in these experiments was supplied by Parke, Davis & Co., Detroit, Mich.

the twentieth birthday. Ten (20.4 per cent) became decompensated before the age of 25, and only five (10.2 per cent) of the 49 died before the twenty-fifth birthday. These figures (Table V) substantiate the above statement.

Among the gravid women there was only one who became decompensated during pregnancy (Case 31). This was a woman whose mitral stenosis was recognized at the age of 18, who first became pregnant at the age of 23, and who delivered three children uneventfully by the age of 29. In the fourth month of her fourth pregnancy, at the age of 30 decompensation occurred, but after conservative management she delivered successfully at term. She lived five years after the fourth pregnancy and died at the age of 35 of congestive heart failure. In this, as well as in 4 other patients where the decompensation occurred two to four months after the last pregnancy, it could not be shown that pregnancy and labor were the cause of the cardiac failure.

#### SUMMARY

An analysis of the life cardiac histories of 49 women with organic heart disease who delivered from 1 to 22 children (average 4.9 pregnancies) as compared with the histories of 41 nulliparous women with similar cardiac lesions revealed that there was little or no difference in the known duration of the heart condition, in the ages at the onset of myocardial failure, or in the ages at death.

The heart lesions were recognized earlier in the parous women, mainly because of the pregnancies. In women with compensated rheumatic heart disease, pregnancy may be undertaken without any added risk. However, it is suggested that women with compensated heart disease be advised to marry early and bear children before the age of 25, if they desire a minimum of risk. In this way, also, they can have a longer period in which to raise their children. Women with heart disease die early because of the natural evolution of the cardiac disturbance and not because of the childbearing.

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Whether vitamin B and D deficiency combined are more important than the B deficiency alone, as a possible cause of eclampsia, remains to be seen.

Eclampsia shows a steady increase in the number of cases beginning in February and reaching its maximum in April according to Kosmak's<sup>8</sup> report of Harrar's observations. This seasonal variation may be due to nutritional influences, for it is during the winter months when fresh food prices are the highest that malnutrition increases. This malnutrition is shown by the fact that most cases of pellagra likewise develop in the late winter and spring.

In the cities of India and China, eclampsia is common while in the rural districts eclampsia is rare according to Dieckmann's<sup>9</sup> report. Again a nutritional factor could account for this difference, for example, in South China the natives eat polished rice in the cities with the result that beriberi is common; on the other hand the farmers eat partially milled rice and beriberi is rare in the rural areas. Eclampsia is quite common in Japan, the Philippine Islands and Hong-kong, and each of these countries report a high incidence of beriberi.<sup>5</sup> The African Colonies of Kenya, Uganda, Tanganyika and others report only a few cases of beriberi and pellagra and in these same colonies eclampsia is rare. The Commonwealth of Australia, with a population of more than seven million people, reported for one year, only one case of pellagra, three cases of beriberi and no eclampsia.

In Germany during the first World War, eclampsia decreased and this fact is puzzling unless the nutritional aspect is taken into consideration. Cowgill<sup>10</sup> states, "In spite of serious food shortage which occurred in Germany during the Great War, it is a fact that beriberi was absent." In other words practically the whole nation was forced to take a diet adequate in vitamin B<sub>1</sub> and the incidence of eclampsia decreased. Titus<sup>11</sup> attributed the low incidence of eclampsia among the Eskimos (who take a high protein, fat diet) to the fact that the temperature of their country is always low and constant. It is of interest to note that an exclusive meat diet is adequate in vitamin B<sub>1</sub> as shown in the experiment when Steffansson and Anderson<sup>10</sup> took an exclusive meat diet for one year and no beriberi developed.

In England and Scotland the incidence of eclampsia is high. Dieckmann's<sup>9</sup> figures are taken from large industrial cities and for England the incidence of eclampsia is 1.61 per cent and for Scotland 1.63 per cent. In these areas pellagra and beriberi are rare diseases but the poorer classes do suffer from malnutrition which may prove to be the chief factor causing such a high incidence of eclampsia. It is reported<sup>12</sup> that the industrial situation has deprived people of first-class proteins, fats, vitamins and that bread, jam, margarine and tea have taken the place of milk, meat, eggs, and fresh fruit. McCance<sup>13</sup> and coworkers report that the vast majority of pregnant women cannot afford the food they need. He adds, "While the intake of total calories and of fat and carbohydrates was little affected by income, it was found, as in other surveys, that protein, animal protein, calcium, phosphorus, iron and vitamin B<sub>1</sub> rose steadily with income." In other words the group of women with the lowest intake of vitamin B<sub>1</sub> show the highest incidence of eclampsia.

If the vitamin B<sub>1</sub> or the B complex is to be used as a preventive measure against the development of eclampsia it should be given as soon as conception occurs and continued through lactation. Early in pregnancy if the patient does not eat well due to nausea, an adequate intake of vitamin B<sub>1</sub> can be maintained by intramuscular injections of thiamine chloride. Clinical experience with a limited number of private patients indicates that such injections of 10 mg. each, given every other day,

and lactation. Spies<sup>7</sup> has found that many patients with pellagra also show signs of thiamin chloride and riboflavine deficiency as well. In other words, eclampsia in the United States occurs most often in those areas where there is a deficiency of the vitamin B complex. No other vitamin deficiency is so localized in the southeastern States. Vitamin D deficiency in the form of rickets does occur in this eclampsia area, but it extends beyond this area, west to the Pacific and north to Canada.

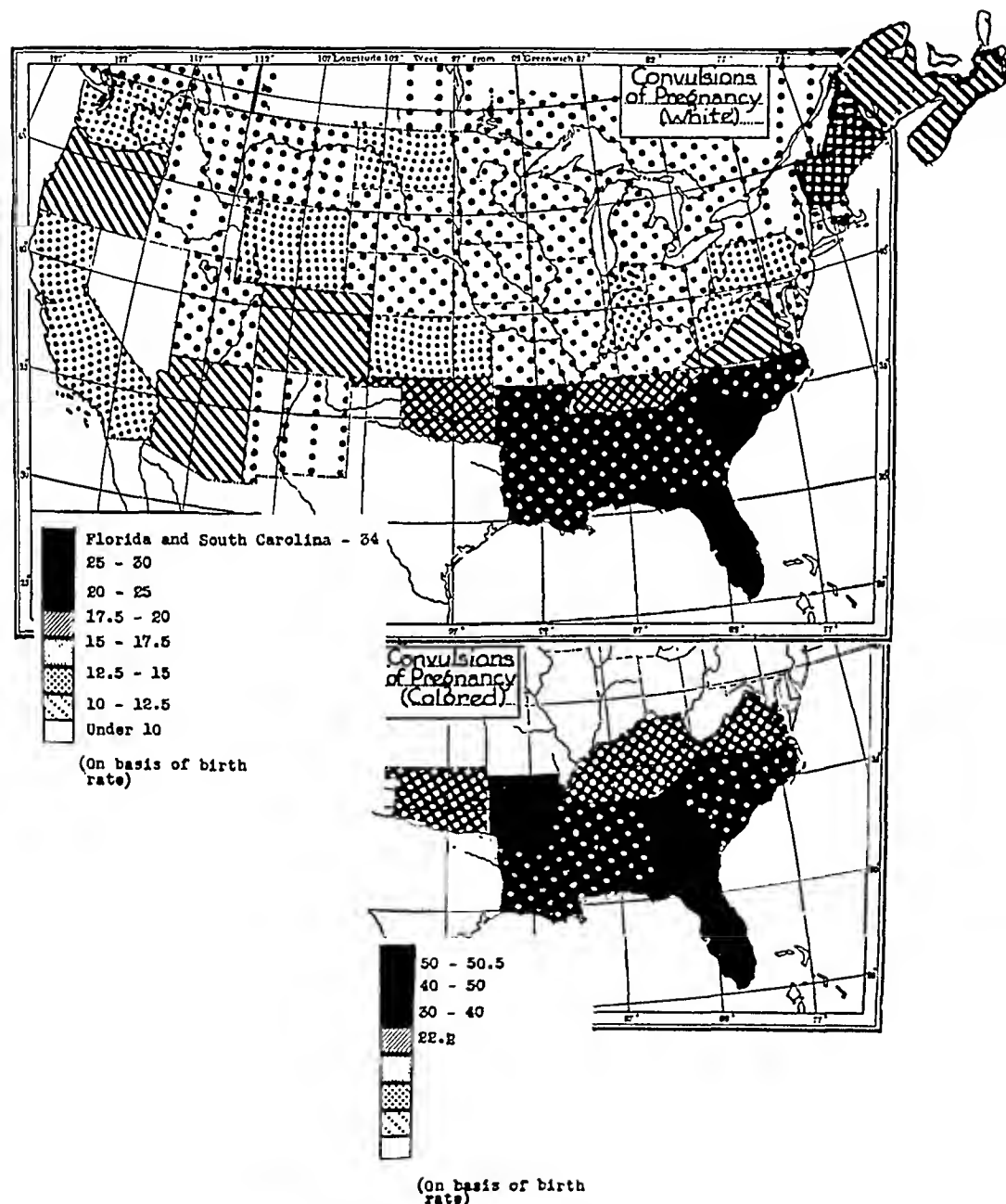


Fig. 1.—Geographic distribution of patients with convulsions of pregnancy. Texas and South Dakota are not in the U. S. Registration area and are therefore not included in the map. (Reproduced by permission from Petersen, William F.: *The Patient and the Weather*, Edward Brothers, Ann Arbor, Mich.)

days of the puerperium. In this series there were 623 multiparas and 377 primiparas. There were 6 sets of twins (Table I).

TABLE I. PRESENTATION AND POSITION

PRESENTATION	NUMBER	PERCENTAGE
Occipitoanterior	837	83.2
Occipitoposterior	110	10.9
Breech	45	4.4
Transverse	2	0.19
Brow	2	0.19
Mentum	1	0.8
Total	1,006*	

\*Six sets of twins.

Parity, duration of labor, method of delivery, weight of the infant and the existence of an intercurrent obstetrical or nonobstetrical complication have a definite bearing in such a study.

*Method of Delivery.*—There were 949 spontaneous deliveries, an incidence of 94.9 per cent. Thirty-two were delivered with the aid of forceps, i.e., 21 low and 11 midforceps applications. The absence of the use of high forceps is noteworthy. Breech extraction was employed in 12, while two were delivered by means of version and extraction. Bag induction was resorted to twice, followed once by breech extraction and another time as the sole operative procedure. The placenta was removed manually three times. There was one cesarean section. In all, 51 patients had some operative interference. This represents an operative incidence of 5.1 per cent—one worth pondering over, in view of the rapidly rising use of so-called “prophylactic forceps” or “outlet forceps” (Table II).

TABLE II. METHOD OF DELIVERY

METHOD OF DELIVERY	NUMBER	PER CENT	OPERATIVE INCIDENCE	
			NUMBER	PER CENT
Spontaneous	949	94.9		
Forceps			32	3.2
Mid           11				
Low          21				
Breech extraction			12	1.2
Version and extraction			2	0.2
Bag induction of labor (2)			1	0.1
1 in a case of breech			3	0.3
Manual removal of placenta			1	0.1
Cesarean section			51	5.1

TABLE III. BIRTH WEIGHTS OF 1,006 INFANTS

NUMBER	WEIGHT		PER CENT
	GRAMS	POUNDS	
37	Under 2,250	Under 5	3.8
632	2,250-3,600	5- 8	65.7
220	3,600-4,050	8- 9	22.8
64	4,050-4,500	9-10	6.6
7	4,500-5,000	10-11	0.7
1	Over 5,000	Over 11	0.1
45	Not recorded		
1,006			Approx. 100

give relief from nausea in about two weeks. Further trial is necessary to verify this response.

#### SUMMARY

1. Daily injections of 6.7 mg. of vitamin B<sub>1</sub> (thiamine chloride) for ten days gave no apparent benefit in patients with pre-eclampsia.

2. The geographic distribution of eclampsia corresponds in many places to the distribution of beriberi and pellagra. This indicates a possible causal relationship between vitamin B<sub>1</sub> or vitamin B complex deficiency and eclampsia.

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## THE TREATMENT OF THE IMMEDIATE POST-PARTUM PERIOD

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THE physiology of the puerperium, with the notable exception, the breasts, is one of involution. Proper uterine involution can be obtained by less accumulation of blood clot and debris, less stasis, less saprophytic invasion, less lowered local resistance, and less infection.

During the first forty-eight hours, the uterus rises approximately 15 cm. above the symphysis.<sup>1</sup> The canal frequently measures 15 to 16 cm. in depth. The large sinuses in the uterine wall are collapsed or thrombosed and about to undergo hyaline and granular degeneration. All this makes an excellent culture medium for saprophytic and pathogenic organisms. Obviously, if the uterine canal can be emptied, the uterine musculature tonically contracted, and the sinuses coapted, there is less possibility for these organisms to flourish. Involution will then proceed rapidly and favorably. The first forty-eight hours, therefore, are very significant.

A review of the treatment of the immediate post-partum period in 1,000 consecutive deliveries at the Coney Island Hospital substantiates the importance of a definitely directed attention to the first two or three

crate in 47.3 per cent, scant in 47.4 per cent, absent in 3.9 per cent, and not recorded in 1.4 per cent. It was rubra in 37.5 per cent, serosa in 51.2 per cent, alba in 9.6 per cent, absent in only 3 cases, and not recorded in 1.4 per cent.

These figures serve to emphasize the desirability of maintaining a tonically contracted uterus without retention of decidual debris during the first seventy-two hours. The free escape of lochia is generally interfered with in a too strongly contracted uterus. Interesting, too, in conjunction with this study is the fact that in a control series<sup>1</sup> lochia rubra was present in 79 per cent of the patients at the time of their discharge from the hospital as compared with 37.5 per cent in the present series (Table IV).

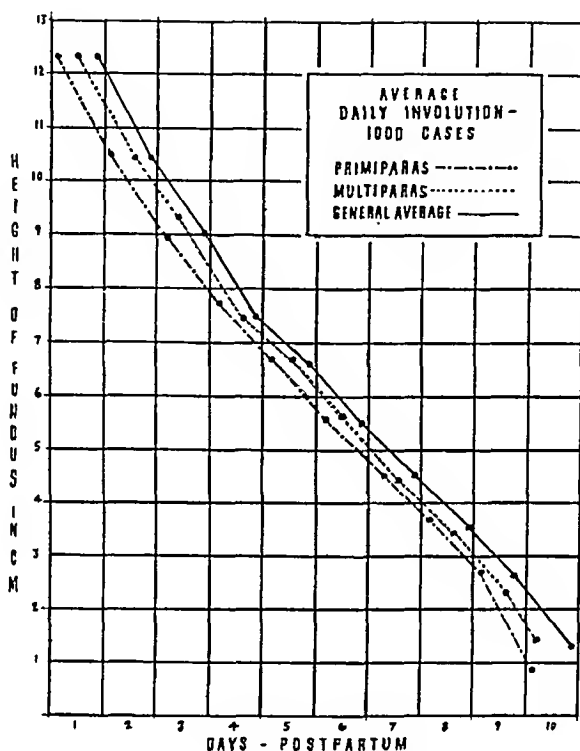


Fig. 2.—Daily involution, 1,000 cases.

TABLE IV. LOCHIA

AMOUNT			CHARACTER			FOUL	
NUMBER		PER CENT	NUMBER		PER CENT	NUMBER	PER CENT
Profuse	0	0	Rubra	375	37.5	14	1.4
Moderate	473	47.3	Serosa	512	51.2		
Scant	474	47.4	Alba	96	9.6		
Absent	39	3.9	Absent	3			
Not recorded	14	1.4	Not recorded		1.4		

*Morbidity.*—Though much may be said about the size of the uterus and the character of the lochia, still the prima indicator for an existing morbidity is the temperature. The standard of 100.4° F. on any two days other than the first, as set down by the American College of Surgeons and generally in use throughout this country, is the one in use in this institution. For purposes of comparison the British Medical Association standard of 100° F. on any two consecutive days other than the first, and the one instituted by DeLee of 100° F. on any day, are included in these tables. However, it does seem as if one were "bending his back to the breaking point" in accepting a first day post-partum rise in temperature to

**Birth Weight.**—Over 30 per cent of the infants weighed between 3,600 and 5,400 Gm. (8 to 12 pounds) (Table III).

**Treatment.**—The groundwork for a normal puerperium is laid in the immediate ante-partum period. Vaginal examinations, unless absolutely indicated are not permitted. Rectal examinations are done as infrequently as is consistent with proper observation of the progress of labor. During the delivery vaginal manipulation, unless part of an operative maneuver, is not countenanced. The Ritgen maneuver is discouraged. Too often rectal contents are smeared over or actually wiped into the relaxed fourchette by overzealous perineal pressure. Observance of little points such as these in the ante- and intrapartum periods bears considerable influence on the outcome of the post-partum period.

Immediately upon the delivery of the placenta, 1 c.c. of ergotamine tartrate (gynergen) is given hypodermically. Rarely is the bleeding severe enough to warrant any other medication. At times pituitrin may supplement ergotamine tartrate. The action of pituitrin, although prompt, is short lived while the ergot alkaloid is prolonged. In fact, it is sufficiently prolonged to allow the uterine musculature to regain some of its tonicity.

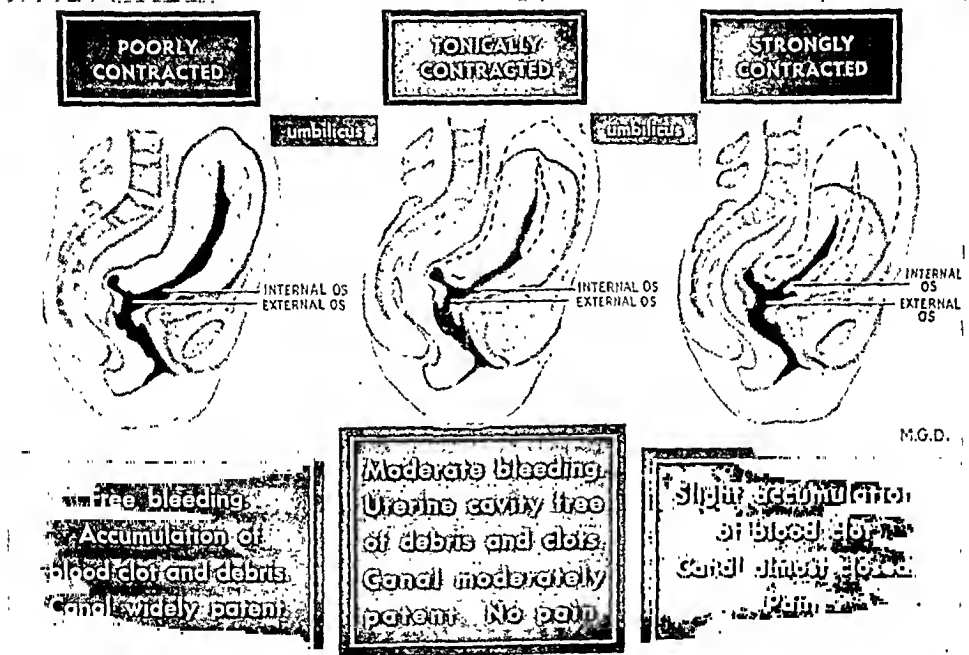


Fig. 1.—Schematic drawing of first day post-partum uterus.

The uterine body is kept tonically contracted by the oral administration of 6 minims of the ergotamine tartrate solution (0.4 mg. of gynergen) every four hours for five doses per day and for the first three days only. Its importance at this time is quite obvious. The uterus instead of remaining 15 to 17 cm. in height for forty-eight hours rises about 12.5 cm. above the symphysis pubis. This seemingly small dose is sufficient to keep the uterine canal empty and the sinuses coapted but not strong enough to interfere with extrusion of any lochia (Fig. 1).

It has been a stereotyped teaching that by the tenth day the post-partum uterus will reach the level of the symphysis pubis. This is a fallacy. In a control series,<sup>1</sup> the height of the puerperal uterus on the tenth day was 5 cm. above the symphysis, while in the current series it reached 1.3 cm. or less than the average fingerbreadth. The primiparous uterus averaged 0.9 cm. and the multiparous 1.4 cm. (Fig. 2).

**Lochia.**—The character and the amount of the lochial discharge was in direct keeping with the rate of involution. In no instance was it profuse. It was mod-



8. The uterine cavity is kept empty, without an undue amount of discomfort, by the systematic oral administration of ergotamine tartrate (gynergen) solution in 6 minim (0.4 mg.) doses for five doses per day for three days only.

9. The bladder, rectum, and vagina should be kept empty. To this end, the patient should be encouraged to empty her bladder every four to six hours, and her rectum daily. A modified Fowler's position for forty-eight hours after the first twenty-four will promote vaginal drainage.

In this study of 1,000 consecutive parturients, the average height of the uterus on the first day post partum was 12.3 cm. as compared with 15.1 cm. in a control series<sup>1</sup> in whom pituitrin alone was used immediately upon the expulsion of the placenta. Further, by the third day post partum, the average height was 9 cm. above the symphysis.

The full significance of this is apparent in

1. The absence of any profuse lochia.
2. The existence of a foul lochia in only 1.4 per cent of all patients including the febrile cases.
3. The presence of a lochia rubra at the time of discharge in about one-third of all the patients, and
4. Most important of all, the controllable morbidity was reduced to 2.5 per cent.

There still remain these 2.5 per cent of obstetric morbidities to be eliminated. This may happen when those responsible for the delivery shall become wholly "obstetric conscious."

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## ROENTGENOLOGIC SURVEY OF CHEST IN PREGNANT WOMEN

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A SPECIAL study of pregnant women by means of fluoroscopic examination of the chest in addition to the usual clinical examination and laboratory tests was instituted about a year ago at the Margaret Hague Maternity Hospital of Hudson County at the request of Dr. Samuel A. Cosgrove. The fluoroscopic examination was selected as the method for preliminary study, because of its simplicity, and all prenatal clinic cases were routinely referred to this department, although some investigators have claimed that the fluoroscope fails to reveal a considerable percentage of positive cases of pulmonary tuberculosis demonstrated roentgenographically.

Boynton<sup>1</sup> and his associates in a survey of students at the University of Minnesota found that 58 per cent of positive cases as shown in the x-ray films were missed on fluoroscopic examination. Of 939 cases with a negative x-ray film,

100° F. as a sign of infection. Dehydration, physical exhaustion, and the sudden flooding of the system with foreign proteins are sufficiently competent causes to produce a slight first day rise in temperature.

TABLE V. MORBIDITY, 1,000 CASES

AMERICAN COL- LEGE SURGEONS STANDARD (UNCORRECTED)		BRITISH MED. ASSN. ADDITIONAL†		DE LEE STANDARD‡ 100° F. ANY DAY				TOTAL MOR- BIDITY, ACCORDING TO ALL STANDARDS	
				FIRST DAY ONLY ADDITIONAL		1 DAY OTHER THAN FIRST ADDITIONAL			
NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
36	3.6*	26	2.6	39	3.9	111	11.1	212	21.2

\*Corrected morbidity 2.5 per cent (25 patients).

†B.M.A., 100° F. on any 2 consecutive days other than first.

‡DeLee, 100° F. or over on any day including first.

Table V shows the uncorrected morbidity according to the standards mentioned. Those classified under DeLee's have been divided into those with only first day temperatures of 100° F. or over and those with similar temperature on any other day other than the first. There were 36 febrile patients in this series of 1,000 parturient women, and uncorrected morbidity of 3.6 per cent. The 36 were distributed among 12 with sapremia, 9 with acute endometritis, 2 with infected episiotomy wounds, 6 with acute mastitis, toxemia of pregnancy in 2, pyonephroses in 2, and one each with cystitis, upper respiratory infection, and pneumonia. With the justifiable elimination of the nonobstetric febrile cases, the corrected morbidity based on the standard of the American College of Surgeons is 2.5 per cent.

#### SUMMARY AND DISCUSSION

A satisfactory puerperium definitely implies careful treatment of the immediate ante-partum and intrapartum periods. The essence of this treatment although well known is worthy of repetition here:

1. Proper toilet for the patient on admission.
2. Pelvic examinations, even though they are rectal, should be done as infrequently as is conducive to the proper observation of the progress of labor. Rubbing the posterior vaginal wall into the cervical canal by overzealous rectal examinations is as harmful as vaginal examinations.
3. Dehydration and exhaustion should be anticipated.
4. During the delivery it is strongly urged that all fingers be kept out of the vagina.
5. The Ritgen maneuver is inadvisable. The extension of the head is better aided by the counter pressure of the thumb and index finger on the outermost points of the bulging perineum.
6. Upon the birth of the presenting part, the anus should be covered with a sterile towel. This prevents the cord from dragging over a contaminated perineum.
7. The action of pituitrin although prompt is short. A more suitable oxytocic at this time is one that will keep the uterus tonically contracted until it has regained some of its tone. This has been accomplished by replacing pituitrin with ergotamine tartrate.

lesions that might become active or reactivated under certain conditions. It is to be noted, however, that the physical examination had not revealed evidence of tuberculosis in any of the cases. The percentage of active or suspicious cases in this group of pregnant women is small in comparison with surveys in other groups, but the diagnosis of tuberculosis in even a small number of pregnant women is important, because of the possible effect of pregnancy on the tuberculous lesion and also because of the possible danger of infection of the infants as well as of other contacts in the home and hospital. The diagnosis of healed tuberculous lesions in the pregnant women is also desirable as it indicates the need of careful supervision and management to minimize the possibility of reactivation of such lesions.

The detection of pulmonary tuberculosis in pregnancy, when it is not indicated by physical signs or symptoms, is of importance to the patient herself, as it enables her to be treated when the disease is in an early stage. The efficiency of collapse therapy needs no further comment on my part. Hill<sup>3</sup> states that the greatest mortality was found among cases diagnosed after termination of their pregnancy, and the least in those women who had tuberculosis before the onset of pregnancy. The inference is that the tuberculosis in properly treated cases improved and not that pregnancy per se does not affect tuberculosis adversely. Close cooperation between the obstetrician and the phthisiologist is an absolute requisite. Where tuberculosis develops after pregnancy has occurred, the sooner lesions are discovered, the sooner rational therapy can be instituted. Therefore, prenatal care should include careful chest examination. All of the pregnant women at the Margaret Hague Maternity Hospital in whom evidence of tuberculosis has been found in this survey have been placed in a special service in collaboration with the Hudson County Tuberculosis Hospital. The early diagnosis of tuberculosis in pregnant women is of importance to the hospital; a certain percentage of these cases, even if it is small, is or may become active with positive sputum and therefore infective. The danger of even one infective case in a maternity hospital, if unrecognized, is great. The same is true of contacts in the home, not only of the newborn infants, but also other children and members of the family who can be protected from infection if the diagnosis is made early and the danger of contagion recognized.

The diagnosis of pulmonary tuberculosis in a large series of cases is of significance from a scientific point of view, namely, to determine the effect of pregnancy upon tuberculosis and the management of both conditions. The opinions as to the effect of pregnancy upon tuberculosis vary widely.

Falls,<sup>4</sup> in a review of the subject, notes that "until recent years it has been held by American medical men that pregnancy has a definitely deleterious effect on tuberculosis." Thus Osler quotes Dubois to the effect that a tuberculous woman might have one baby in safety, a second possibly, and a third, never. Bacon states that 33 per cent of pregnant women with active tuberculosis do not survive the first year after delivery. These statements, however, do not appear to be in line with the newer concepts of tuberculous therapy. Matthews and Bryant,<sup>5</sup> in 1930, stated that on the basis of their studies at Trudeau they consider pregnancy to be

21 per cent were thought to have pulmonary lesions in the fluoroscopic examination. In 166 cases with positive x-ray findings, the fluoroscopic findings agreed in only 42 per cent of the cases. They state, however, that the work was done by regular staff physicians experienced in fluoroscopy but not roentgenologists. In this connection, the multitude of errors committed by many general practitioners, with no special training in fluoroscopy but who make it a part of their regular office practice, is to be deplored.

Fellows and Ordway,<sup>2</sup> reporting on fluoroscopic and simultaneous x-ray examinations carried out by the Metropolitan Life Insurance Company, found that the former revealed pulmonary lesions in 87 per cent of those shown to be positive by the x-ray film. They note also that physical examination revealed only 36 per cent of the x-ray positives. Sampson and Brown<sup>3</sup> of Trudeau Sanatorium, on the basis of their findings, express the opinion that in the x-ray study of the chest in adults, who show no physical signs of tuberculosis, few tuberculous lesions of clinical importance are missed fluoroscopically. They emphasize the importance of experienced examiners, those experienced not only in x-ray work in general, but particularly in fluoroscopic diagnosis of the chest. In such hands, they believe that not over 3 per cent of tuberculous lesions are missed. Physical examination, on the other hand, failed to reveal signs of tuberculosis in 39.6 per cent of the cases found to be positive by the x-ray.

At the Margaret Hague Maternity Hospital this study was made by trained examiners with special experience in fluoroscopic diagnosis of chest diseases. Our results indicate that the accuracy of the fluoroscopic diagnosis of pulmonary tuberculosis is 91 per cent and that very few, if any, lesions of clinical importance are missed by this method. The simplicity and rapidity of the fluoroscopic method is of definite advantage in the examination of large numbers of patients or in any form of group survey. The radiograph can then be employed for a further study and classification of the lesions found.

From May 1, 1938 to May 1, 1939, we have made 2,834 fluoroscopic examinations of pregnant women at our prenatal clinic. There were 238 cases checked by subsequent x-ray examinations and these revealed lesions as enumerated below.

1. Pulmonary Disease	{	a. Active tuberculosis, 3 cases or 0.1 per cent	
		b. Inactive tuberculosis, 18 cases or 0.6 per cent	
		c. Suspicious tuberculous disease, 14 cases or 0.5 per cent	
		d. Healed primary tuberculosis, 95 cases or 3.2 per cent	
		e. Nontuberculous lesions, 10 cases or 0.35 per cent	
2. Cardiac Disease	{	a. Definite cardiac lesions in 55 cases or 1.9 per cent	
		b. Suspicious cardiac lesions in 23 cases or 0.8 per cent	
3. Miscellaneous Abnormalities	{	a. Azygos lobe	2
		b. Spine	5
		c. Ribs	6
		d. Thyroid	1
4. No Pathology	19 cases		
5. Total Cases	251*		

Considering the cases of pulmonary tuberculosis revealed by the fluoroscope and checked on the x-ray film, the figures show an incidence of 4.5 per cent for the entire series of women examined. Of these, it is true, but a small percentage showed definitely active lesions, approximately 0.1 per cent of the series. Another 0.6 per cent represented

\*The difference between 251 and 238 is accounted for by the fact that 13 cases presented double pathology.

outline and its measurements were derived. Supplementary clinical follow-ups and electrocardiographic studies were made by the Cardiology Department.

It might be of interest to state that all the cases which were referred for roentgenologic heart examination were found subsequently to have a cardiac lesion either of an active or a silent type, requiring special care and management, and in this way it is safe to say that this method is an advantage in prenatal care.

While here the question of infection is not involved, there is, nevertheless, the important problem of management, both of the cardiac lesion and the pregnancy, to be considered. Hence the fluoroscopic study of the chest in pregnant women has a twofold importance, but the early diagnosis of tuberculosis is of the greatest significance.

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### CANCER AND FIBROMYOMAS OF THE UTERUS\*

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UTERINE fibroids may precede and coexist with cancer of the uterus. References to this association, estimates of its frequency and discussions of the etiologic relationship have appeared in published reports.

The material here presented was studied to compare findings with results of other investigations. In addition I have been impressed by failures of recognition of this "sympiotic" growth clinically and the attendant harmful possibilities. Thus the apparent need for emphasis upon the practical phase was evidenced.

This report presents an analysis of the clinical and pathologic records of 476 fibromyomas and 172 malignancies of the uterus. All material was unselected, histologically confirmed and from the Gynecologic and Oncologic Departments of the Indianapolis City Hospital for the five-year period July 1, 1934 to July 1, 1939.

Considerable interest has been shown in the possible etiologic relationship between fibromyomas and uterine malignancies, both corporeal and cervical.

\*Read at a meeting of the American Association for the Study of Neoplastic Diseases, Washington D. C., Sept. 9, 1939.

distinctly harmful to tuberculous women. On the other hand, Ornstein<sup>6</sup> and his associates in a study of 85 cases of pregnancy in tuberculous women found that pregnant women did as well as nonpregnant women with tuberculosis. Barnes and Barnes<sup>7</sup> also conclude that pregnancy did not exert an ill effect on sanatorium cases. Hill's<sup>8</sup> opinion has been previously noted. Cohen,<sup>9</sup> of the University of Liverpool, from a review of the literature on the subject and his own investigations, considers that pregnancy has no ill effect on inactive lesions, but may aggravate the disease and "accelerate its fatal termination" in active lesions; this he states depends to some extent upon the type of disease present. Falls is also of the opinion that each case of pregnancy in a tuberculous woman "should have individual consideration, and the most important factor is the type and progressive tendency of the lesion." Cohen, in concluding his review, says, "Advance in our knowledge of the interrelationship of pregnancy and tuberculosis will come not from ex-cathedra pronouncements of accepted authority but from the careful collecting of opposite and adequate data and their subsequent unprejudiced analysis."

Aside from the indirect benefit of adequate control and treatment of our patients, the diagnosis of tuberculosis in pregnant women at the Margaret Hague Hospital is designed for the collecting of adequate data regarding the problem of pregnancy and tuberculosis. We plan to carry on the work of fluoroscopic examination of all prenatal cases coming to our clinic with subsequent radiographic check-up as often as deemed necessary; and careful supervision and treatment of those who show evidence of tuberculosis. But this is not all; we plan to keep these women under supervision and control for a period of from three to five years, through subsequent pregnancies, and thus hope not only to provide adequate treatment for their tuberculosis and delivery under hospital conditions, but also to collect definite information on a large series of cases which will be of aid in answering the question as to the effect of pregnancy on tuberculosis, and the proper conduct of the case when a tuberculous woman becomes pregnant or tuberculosis is found after pregnancy is established.

I have emphasized our findings in the diagnosis of tuberculosis in pregnant women, because this phase is of paramount importance, but the value of the cardiac findings in this series is not to be overlooked. The demonstration of even a minimal cardiac lesion is of importance in the care of a pregnant woman.

In fluoroscopic study of the heart, which is made in three different positions, attention is directed toward pulsations, size, position, and contour of the heart. To evaluate these, the roentgenologist has to take into consideration normal physiologic changes during pregnancy which have an influence especially on the position, size, and contour of the heart. The principal changes we found were a more prominent left auricular-pulmonic curve, especially in the left oblique position, slight tendency toward a mitral configuration, and increased density of the aortic shadow. These physiologic alterations are marked in the third and fourth months, when the pregnant woman tries to adapt herself to the increased burden and in the last month of pregnancy when the mechanical influence of the increased intra-abdominal pressure comes into play. Abnormal findings were therefore suspected in all cases in which signs outside of these physiologic changes were noted, and these were checked by teleroentgenographic examinations in which the cardiac

frequency. However, many of these adnexal changes may be interpreted as the direct result of the presence of the fibroids within the uterus. Indeed, such interpretation has been accepted for some time past.

The intrauterine lesions associated with fibroids occurred with the same relative frequency in the cases without adnexitis. Therefore adnexal inflammation cannot logically be held responsible for these associated lesions within the uterus. This fact does not negate the relationship between increased estrin production and the uterine proliferative lesions, but adds doubt as to the importance of infection in initiating the imbalance.

TABLE II. INTRAUTERINE PATHOLOGY ASSOCIATED WITH FIBROMYOMAS

Supracervical hysterectomies	374
Total hysterectomies	102
	Total 476
Endometrial hyperplasia	54 or 11.0 per cent
Endometrial polyps	37 or 7.7 per cent
Hypertrophy of uterus	25 or 5.2 per cent
Glandular hypertrophy of endometrium	24 or 5.0 per cent
Chronic endometritis	14 or 2.9 per cent
Adenomyoma	13 or 2.7 per cent
Adenomyosis	10 or 2.1 per cent
Adenomatous cervical polyps	4 or 0.8 per cent
Atrophy of uterus	2 or 0.4 per cent

Intrauterine pathology associated with fibromyomas in 476 cases was recorded. As noted, endometrial hyperplasia occurred in 11 per cent. If hyperplasia occurs as an index of increased estrin secretion, it is difficult to explain the etiology of the fibroids in this group on the basis of excess estrin secretion alone. This finding agrees with the observations of Kanter and others previously quoted.

The failure of maturation of the follicles has been suggested by Witherspoon as the cause of sterility related to fibroids. In this series of 448 cases submitting uterine tubes and ovaries, 144 were sterile or denied pregnancy, an incidence of 32 per cent. Fourteen of these patients were single. Of this sterile group, 25, or 17 per cent, failed to demonstrate pathology of the tubes or ovaries; atretic follicles as well as inflammatory changes were absent. Retention cysts were present in 21, or 14 per cent. The remaining 98, or 69 per cent, showed salpingitis of one form or another, and sterility might have resulted from the relative or absolute tubal closure.

Uterine fibromyomas and corporeal and cervical cancer are so common in occurrence that it would seem strange if they did not appear together. Speculation as to the full significance of their simultaneous presence has provoked much discussion. Many investigators have reported statistics supporting their belief that malignancies occur more frequently in the presence of myomas than in the nonmyomatous uterus.

Martzfloff<sup>5</sup> collected statistics from various investigators; the composite showed an average of 2.23 per cent corporeal and 1.5 per cent cervical cancer complicating fibromyomas. Only one author (O. Frankl) reported the usual relative incidence of occurrence of the two forms, corporeal 0.53 per cent and cervical 3.3 per cent.

The connection between tumor growth and hormonal factors has provoked discussion. The rapid growth of myomas coincident with the hyperestrinism of pregnancy and the regression during puerperal and menopause states is an old clinical observation. Witherspoon<sup>1-3</sup> attempted to correlate associated infection and endocrine imbalance as agents in the etiology of myomatous growth. He emphasized the infectious origin of follicular retention cysts and concluded that the resulting hyperestrinism was the most active exciting cause of fibromyomas. The coexistence with fibroids of hyperplasia of the endometrium, adenomyosis and endometriosis was predicated upon a similar basis.

Evidence contrary to the broad acceptance of this theory has been presented. Kanter and others<sup>4</sup> reported a lack of consistency in the uterine and adnexal findings coexistent with fibromyomas. They concluded that hyperestrinism is not the sole factor in the production of these lesions.

TABLE I. ADNEXAL PATHOLOGY ASSOCIATED WITH 448 CASES OF UTERINE FIBROMYOMAS

	NO.	PER CENT		RATIO
		GROUP	TOTAL	
<i>No adnexal pathology</i>	61	100.0	13.6	1:2.6
Uterus with fibroids <i>and</i> associated lesions	17	27.8	3.8	
Uterus with fibroids <i>no</i> associated lesions	44	72.1	9.8	
<i>With adnexal pathology</i>	387	100.0	86.4	1:2.58
Uterus with fibroids <i>and</i> associated lesions	108	27.9	24.1	
Uterus with fibroids <i>no</i> associated lesions	279	72.0	62.2	
Associated lesions, uterine tubes and ovaries				
1. " " "	171		38	
2. " " "	106		23	
3. " " " retention cyst ovaries	52		11	
4. Retention cyst ovaries	43		9	
5. Other adnexal lesions alone	15		3	
Atrophy of ovaries (8), ovarian dermoid cyst (3), bilateral fibromyoma of ovaries (1), papillary cystadenoma of ovary (1), Brenner tumor of ovary (1), corpus luteum cyst (1).				
Associated with Lesions 1 to 4				
Granulosa cell tumor of ovary (1), dermoid cyst of ovary (5), pseudomucinous cystadenoma of ovary (1), adenocarcinoma of ovary (1), ovarian fibroma (2), endometriosis of appendix (1).				

In this series, specimens of the ovaries and uterine tubes were examined grossly and microscopically in 448 cases. Witherspoon reported a group with almost 100 per cent salpingitis and cystic oophoritis. Analysis of the series here presented revealed adnexal pathology in a high percentage (86.4 per cent) although ovarian cystic disease was found in only 20 per cent. Proliferative intrauterine pathology was associated with fibromyomas in approximately 28 per cent. Endometrial hyperplasia, endometritis, adenomyosis, hypertrophy of the endometrial or myometrial elements, alone or in combination, were noted as frequently (in almost exact ratio) in proportion, however, in the group without adnexal pathology.

The high incidence of adnexal pathology (86.4 per cent) suggests a relationship to the fibromyomas, the two occurring together with such



corporeal and 8.2 per cent of the cervical cancers which had associated fibroids. Both uterine sarcomas occurred in fibroid uteri.

Of 170 uterine cancers, the uterus was available as a specimen in 43, 14 of the corporeal and 29 of the cervical cancers. Cancer diagnosis was by biopsy specimen alone in 117 patients, who received irradiation as the treatment of choice. Of the 29 uterine specimens available, showing cervical cancer, 13 contained fibroids, and comment in explanation of this fact will be made later.

The incidence of cervical cancer in this series of fibromyomas is relatively high, but it may be presumed that this incidence would have been further elevated if uterine specimens had been available in the 117 diagnosed by biopsy alone, as apparent fibroids were palpated clinically in many instances.

Dublin<sup>9</sup> has estimated that the mortality rate among colored females from cancer of the female genital organs is about 50 per cent higher than among white females at all ages combined. In this group there were 2.8 times more uterine malignancies in white than colored, with equally available beds. Of the 18 uterine cancers with fibroids, 8 were colored and 10 white. In the uncomplicated fibroid cases (476), there were 3.3 times more colored than white patients, in spite of the fact that white beds on female surgery are double those of colored.

The immediate practical value of this study is in determining the factors which may aid us in cancer prevention and control in the individual patient.

The preoperative investigation of patients with fibroids should always be thorough. The presence of fibroids may definitely obscure related or coexistent pathology.

TABLE IV. RESIDUAL CANCER

	NO. CASES
Malignancy of cervix stump recognized postoperatively	10
Supracervical hysterectomy for fibroids	7
Salpingo-oophoritis	3
Cervical carcinoma recognized by pathologist after total hysterectomy	3
For fibroids	1
For adnexitis	2
Malignancy of cervix stump late after supracervical hysterectomy	6

This fact is evidenced by the number of patients in this series with residual cancer following operative procedures for fibroids. Eight patients, an incidence of 1.2 per cent of the entire series, presented this complication. An additional 5 patients exhibited residual cancer following surgery for other pelvic pathology, the total incidence of immediate residual cancer being 2.6 per cent.

These omissions of preoperative investigation were made by men thoroughly trained and with years of experience in clinical and surgical gynecology. The diagnosis of cancer when present is relatively easy. This fact further emphasizes the general need for stimulation of a "cancer conscious" attitude within the profession as well as among laymen.

Many authors report a much higher frequency of cancer in the myomatous uterus than the usually accepted 2 to 4 per cent. Falls<sup>6</sup> recently estimated cervical and corporeal cancers, totaling 9.9 per cent in a series of uterine fibroids. Others present contrary evidence. Von Geldern<sup>7</sup> in a careful analysis of hysterectomy and autopsy material failed to reveal an increase in the incidence of cancer in the myomatous over the nonmyomatous uterus. Contrasting opinions demonstrate the difficulty of accurate analysis and correct interpretation of statistics relative to this supposed relationship. There is evidenced a growing belief, however, in the etiologic relationship between corporeal cancer, fibromyomas and other proliferative growth activities within the uterus. The status of cervical cancer in this problem seems to remain controversial.

Evidence that the hormone factor is most significant in the etiology of proliferative growth has accumulated. The only known cause of endometrial hyperplasia is continued hyperestrin secretion. Novak and Enmei<sup>8</sup> in a most excellent discussion of the variable features and gradations of endometrial hyperplasia present evidence pointing to a relationship of some sort between postmenacme hyperplasia of the endometrium and corporeal adenocarcinoma. It is a regrettable feature that, in this series of corporeal cancer here presented, the noncancerous endometrium was not studied.

Determinations of the incidence of cancer complicating fibroids are of interest but of value only in relation to the group studied. It is impossible to state the frequency of fibroids since only hospital patients are studied. Differences in social, economic, and racial status occur. Thus the conditions present control the statistics to a great extent.

TABLE III

<i>Per Cent Fibromyomas Complicated by Malignancy</i>			
Fibromyomas without malignancy		476	
Fibromyomas with malignancy		20	
	Total	496	
Fibromyomas and:			
Corporeal carcinoma	5 or 1.0	per cent	
Cervical carcinoma	13 or 2.62	per cent	
Sarcoma of uterus	2 or 0.40	per cent	
Total	20	4.02	per cent
<i>Per Cent Malignancies Complicated by Fibromyomas</i>			
	NO.	FIBROIDS	PER CENT
Malignancies:			
Corporeal cancer	18	5	27.7
Cervical cancer	152	13	8.2
Sarcoma of uterus	2	2	100.0
Total	172	20	11.6

In this group there were 476 cases of fibromyomas and 172 instances of malignancy of the uterus. Malignancy and fibroids coexisted in 20 patients, 4.02 per cent incidence. Eighteen uterine carcinomas complicated fibroids, an incidence of 3.62 per cent. Five of the cancers were corporeal and 13 cervical, an incidence of 1 and 2.62 per cent, respectively.

Of the 172 uterine malignancies 20 were associated with fibroids, an incidence of 11.6 per cent. There were 170 carcinomas of the uterus, 18 being corporeal and 152 cervical. There were 27.7 per cent of the

3. If endometrial hyperplasia is an index of increased estrin secretion, the low incidence of this finding with fibroids indicates the necessity of considering other factors in addition to hormonal in the etiology of fibroids.

4. A relatively high percentage of cervical carcinoma was found in fibroid uteri in this series. Factors are presented in discussion which influence statistics showing the association of fibroids and cancer.

5. The number of residual cancer cases indicate that from the standpoint of the individual patient in dealing with fibroids the primary consideration should be the determination of the presence or absence of malignancy.

6. The problem of treatment of fibroids, or any pelvic disease, presents also the responsibility of eliminating potential sources of future cancer development.

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### INTESTINAL INTUBATION IN GYNECOLOGIC INTESTINAL COMPLICATIONS

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**D**URING the past year intestinal decompression with the Miller-Abbott tube<sup>1</sup> has been used at Lakeside Hospital as an adjunct in the management of over forty patients with intestinal obstruction, either mechanical or paralytic. About 25 per cent of these cases had primary gynecologic disorders and the intestinal obstruction was a complication. Generally the intestinal complication contributed more to the patient's discomfort and to the gravity of the prognosis than the gynecologic disorder.

As these gynecologic patients form such a large part of the general group of intestinal obstructions, it seems timely to point out the value of intestinal decompression in their management. Although the series is too small for a statistical survey, we feel this method will decrease mortality. The value of decompression of the upper intestinal tract has been established by Wangenstein,<sup>2</sup> and intestinal intubation extends this method to permit decompression of the intestine to any depth. The technique of intubation has been described by Miller, Abbott, Johnston and others.<sup>1, 3-5</sup>

Intubation in the intestinal complications of gynecologic disorders may be considered under two headings: (1) preoperative use and

In most instances the failure to make a careful and complete pre-operative investigation was caused by the obvious presence of a fibroid uterus which clinically overshadowed the more important cancer. The records showed lack of careful consideration of the history and omission of detailed inspection and palpation of the cervix. Cervical biopsy was greatly neglected in this series.

Progressive metrorrhagia intermitting with foul leucorrheal discharge may accompany certain types of fibroids. In such instances, however, endometrial biopsy should precede surgery. The clinical recognition of carcinoma in a myomatous uterus may have a momentous bearing upon the patient's welfare. Adequate treatment may be neglected by assuming that the patient has only fibroids.

The occurrence of cancer in the cervical stump late after hysterectomy introduces a problem in cancer control. Six instances occurred in this series, three of which gave a history of removal of corpus for fibroids, but are not included in the fibroid with cancer series. Histologic study was not available. This incidence is too great to be neglected. Due consideration should be given this possibility in each individual case, and the conviction that cancer and fibroids have no connection should not cause neglect of an obviously diseased cervix.

Limitation of time permits little discussion of the total versus supracervical hysterectomy procedures, about which there is still much controversy. I personally lean strongly toward total hysterectomy wherever possible, and am not convinced that the added risk is great.

Pfaff,<sup>10</sup> in 1936, examined the records of three Indianapolis Hospitals for the five years preceding. His statistics showed 1,691 supracervical hysterectomies with a mortality rate of 3.29 per cent and 567 total with mortality of 3.3 per cent.

COMPARATIVE MORTALITY (PFAFF)

	HOSP.		HOSP.		HOSP.	
	A	MORT.	B	MORT.	C	MORT.
Supracervical	273	2.5%	760	2.7%	658	4.3%
Total	227	2.6%	191	3.2%	149	4.5%

If one prefers supracervical hysterectomy, associated apparently benign cervical lesions should be treated by actual cautery, endothermy, or classic surgical methods, and I might add, accompanied by biopsy whenever possible.

The treatment of uterine fibroids by irradiation without preliminary endometrial biopsy is to be condemned.

#### CONCLUSIONS

1. The clinical and pathologic records of 476 cases of fibromyomas with associated adnexa in 448, and 172 malignancies of the uterus were reviewed.

2. Evidence confirmed the high incidence of adnexal pathology associated with myomatous uteri, but adds doubt as to the relationship between adnexal inflammation and intrauterine lesions associated with fibroids.

tion of a small amount of thin barium suspension through the tube showed that here the advance was stopped by a fixed, sharp turn in the terminal ileum.

Pelvic examination at this time revealed a symmetrical, freely movable, right-sided suprapubic mass about 7 cm. in diameter and a smaller left adnexal mass inseparable from the uterus. Pelvic cellulitis had decreased.

Because of the high degree of intestinal obstruction, operation was deemed advisable even though from the gynecologic aspect it was desirable to allow the pelvic inflammation to become more quiescent. At operation the pelvis showed evidence of subacute and chronic inflammation. On the right side there was a hydrosalpinx. On the left side there was a tuboovarian inflammatory mass in the cul-de-sac, with dense and vascular adhesions. A loop of upper ileum was acutely kinked and solidly attached to the latter mass. The loop was deflated with the tube passing through it, but the intestinal wall was thickened proximal to the adhesion. A more distal loop near the terminal ileum was also adherent to the adnexal mass, this being fixed in position but not obstructed. Thus the preoperative localization of the intestinal obstruction was confirmed.

Supracervical hysterectomy and bilateral salpingo-oophorectomy were done without difficulty, the intestinal adhesions freed and the abdomen closed without drainage. Her convalescence was uneventful. The tube was left in place with suction maintained intermittently until the fifth day. There was absolutely no clinical evidence of postoperative ileus. The highest postoperative temperature was 38.3° C., during the first two days. An enema was effectual on the fourth day and subsequently the patient had spontaneous normal stools. She was discharged on the eleventh day, and in the subsequent twelve months has been symptom free.

This case illustrates several advantages of preoperative intubation.

1. It relieved all symptoms which were due to intestinal obstruction from bowel involved in a pelvic inflammatory disease.

2. An immediate operation was safely delayed on a patient in poor condition. During this interval the patient received an adequate fluid, chloride, and dietary intake with improvement in her condition.

3. Since the surgical procedure was made elective, satisfactory preliminary treatment of the pelvic disease was possible. The operation was technically simplified as the pelvic infection was quiescent and the intestine was completely deflated.

4. During this interval the diagnosis was more accurately established.

5. The postoperative course was probably smoother, as it is possible that had not intestinal drainage been available some degree of postoperative ileus would have occurred, considering the amount of handling of intestines required at operation.

Although operation was necessary in this case, in others in which the actual mechanical intestinal obstruction is less, the adhesions less fibrous, and the acute symptoms largely due to paralytic ileus, operation may not be required. The relief of distention while the pelvic inflammatory process is subsiding may entirely relieve the intestinal obstruction. Similarly, intestinal intubation may relieve the occasional obstruction following heavy irradiation of the pelvis for neoplasm when surgery is obviously contraindicated.

#### POSTOPERATIVE USE

The patient, a 45-year-old white woman, had enjoyed good health except for uterine bleeding of several months' duration. Physical examination was negative except for a large fibrotic uterus which was removed without difficulty, total hysterectomy being done. There was no visible bleeding upon closure. The patient withstood the procedure well and the immediate postoperative recovery was satisfactory, although the temperature rose to 38° C. and fluctuated around this level. Water

(2) postoperative use. The first group also includes those cases of pelvic inflammatory or neoplastic disease with intestinal complications in which surgical procedures do not become necessary. A case summary in each group will illustrate the value of this procedure.

#### PREOPERATIVE USE

A 43-year-old woman had occasional attacks suggestive of partial intestinal obstruction for four years. One week before admission a similar but more severe attack began, characterized by cramplike lower abdominal pain, distention, and persistent vomiting. It was not relieved by vigorous self-administered cathartics which had helped previous attacks. Her gynecologic history was noncontributory except for sterility of many years' duration.

Physical examination revealed an acutely ill, dehydrated patient. Her temperature was 38.2° C., pulse 100, respirations 24, and blood pressure 120/70. Positive findings were limited to the abdomen which was moderately distended and tympanitic. There was some rigidity and tenderness in both lower quadrants. On auscultation peristaltic sounds were increased in frequency. There was profuse vaginal discharge, and on pelvic examination there was tenderness and induration, more marked on the left side.

Laboratory data revealed a leucocytosis of 13,500 and 75 per cent hemoglobin (Sahli). There were a few white blood cells and a slight trace of albumin in the urine. The maximum sedimentation rate was 2.2 mm. per minute. Urethral and cervical smears were negative for gonococci. A roentgenogram of the abdomen showed several distended small intestinal loops localized in the left side and some gas in the colon.

The impression of most of those who saw the patient was that she had a pelvic infection with partial intestinal obstruction. Conservative treatment consisting of daily Elliott's treatments, continuous hot stupes to the abdomen, and supportive measures was instituted. Constant Wangenstein gastric drainage was started, but, since the distention decreased and she had a normal stool, this was discontinued after twenty-four hours.

Her course was favorable until the eighth day when her lower abdominal cramplike pains recurred. The temperature spiked to peaks of 39.7° C. and the pulse rose to 120. The distention increased rapidly, bowel movements ceased, and vomiting began. Peristalsis first increased in frequency and then decreased. A roentgenogram showed considerable increase in the amount of gas in the small intestine.

Apparently the bowel had become completely obstructed. Surgical intervention was not desirable in the face of the active pelvic infection, and decompression with the Miller-Abbott tube was started. Within twenty-four hours her temperature dropped, reaching a peak of only 38.3° C. The pain and vomiting ceased and distention was relieved. It was felt that an immediate operation could be delayed without danger to the patient.

She tolerated the tube well and after the first day she took adequate fluids, and a 2,000-calorie, special low residue diet<sup>7</sup> by mouth. Oral salt intake was adjusted to maintain normal blood chlorides. Her temperature fell gradually and after one week reached normal and remained so for the subsequent week. During this interval local treatment of pelvic cellulitis was continued. Her intestine remained decompressed, although she had no spontaneous bowel movements and enemas were ineffectual.

Within twenty-four hours after the intestinal tube was started, the tip had reached the left midabdomen in the region where the dilated small intestinal loops had been present for at least eleven days as shown by roentgenograms. The tip of the tube stayed in this region about ninety-six hours while constant drainage was maintained. Even after the tip had left this area a small amount of gas persisted in these loops. This area appeared to be in the lower jejunum and the site of the partial obstruction responsible for her long history of intestinal trouble. After the tube tip left this area, advance continued regularly until it reached the terminal ileum where it again stopped. Investigation of this area by the injec-

Contraindication to and dangers in the use of the intestinal tube have been elaborated.<sup>3-5</sup> Probably the greatest risk is the possibility that immediate surgery might be delayed in obstructed intestine to which the blood supply has been endangered. Such cases of strangulated intestine within the abdominal cavity can usually be recognized by the clinical picture<sup>4, 8</sup> of an abrupt onset, rapidly progressive severity and findings of peritoneal irritation. Where endangered blood supply is not evident at the onset but such an event occurs after the tube is started, we feel that it can be recognized. With the tube advancing and deflation progressing satisfactorily, signs of peritoneal irritation, a rise in temperature, pulse or leucocyte count indicate probable strangulation. Four such cases have been encountered in which decompression was begun by intestinal intubation and strangulation subsequently developed. These were recognized and laparotomy was immediately performed. In only one had the vascular change progressed enough to require resection of some intestine. All patients recovered.

The danger of fluid and mineral loss by a prolonged period of intestinal drainage is overcome by adjusting the salt intake to maintain normal blood chlorides (usually 8 to 15 gm. daily) and adjusting the fluid intake to obtain a voided output of 1,000 to 1,200 c.c. daily. In almost all instances the salt and fluid can be administered orally, and at the same time an adequate calorie and vitamin dietary intake can be given.<sup>7</sup>

The question of production of esophageal erosions by the tube also arises. The majority of patients do not complain excessively of its presence. Preservation of the general state of nutrition and frequent shift in position of the tube with a normal oral intake may make erosion less likely to occur than in an undernourished patient who is not taking anything by mouth.

#### CONCLUSION

1. In a series of over 40 cases of intestinal obstruction due to either mechanical or paralytic ileus, about 25 per cent were complications of primary gynecologic disorders.

2. This group of cases offers an ideal field for the use of intestinal intubation with the Miller-Abbott tube, both as a method of treatment and for diagnosis.

3. Cases are cited illustrating the advantages obtained by using the intestinal tube as an adjunct in the treatment of intestinal complications before and after operation in gynecologic patients.

4. It is hoped that this adjunct will lower the mortality which at present is high in this group of cases.

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was given the first day, clear liquids the following day. On the second day nausea and abdominal pain began. The abdomen showed progressive increase in distention and vomiting occurred. The wound was probed on the third day, found to be infected and drained purulent material subsequently, but the temperature remained elevated. By the fifth day the distention was quite severe in spite of the use of enemas and Wangensteen gastric drainage. Rectal examination revealed a firm, tender mass in the cul-de-sac, bulging into the rectum. On the seventh day this was opened through the vagina, a large amount of bloodstained fluid streaked with pus evacuated, and a drain was inserted.

She did not improve and the fourth day after the incision and drainage of the infected pelvic hematoma, her condition was critical. The abdomen was markedly distended, practically no peristaltic sounds were audible and the rectum was collapsed. Roentgenograms of the abdomen showed numerous distended loops of small intestine filled with gas and fluid with a "ladder" pattern. An enterostomy was considered, but, as this was all that could be attempted in view of her critical condition, it was felt that intestinal intubation would accomplish the same result without the risk of additional surgery.

An intestinal tube was started and there was profuse drainage of intestinal fluid and gas contents for several days. The distention decreased markedly, the temperature dropped to around a 38° C. level, and the patient improved considerably. After the tube was well advanced in the intestine, the patient took adequate fluids, chlorides, and the low residue diet by mouth, so that parenteral fluids which had been required for the first eleven postoperative days were no longer needed. The tube was kept in place for eighteen days. Every few days she was given a trial without the tube by discontinuing the suction and deflating the balloon. However, each time this was done her discomfort increased and distention reappeared. She had no spontaneous bowel movements and frequent enemas were ineffectual until the seventeenth day, when she began to have spontaneous bowel movements.

Fluoroscopic examination with injection of barium into the intestine through the tube at this time showed the tip to be about 25 cm. proximal to the cecum. There was evidence of irritability of the terminal ileum and displacement in its position out of the pelvis but no point of obstruction to the cecum. Some barium given by enema showed areas of narrowing in the sigmoid colon which appeared to be due to an extrinsic lesion. It is very likely that the sigmoid colon had been the site of the obstruction which was relieved as the infection subsided.

The tube was removed on the eighteenth day, and the patient's subsequent course was uneventful, except for occasional mild diarrhea which was attributed to irritability in the narrowed areas of the sigmoid. This soon disappeared, the vaginal discharge ceased and the infected wound healed. The patient's course for the seven months since discharge from the hospital has been uneventful.

This case illustrates how intestinal intubation can be used in post-operative complications of pelvic surgery.

1. It was used as a method of treatment with excellent clinical improvement.

2. The tube produced the results of an enterostomy without the necessity of an operation. The "intestinal tube enterostomy" is a cleaner, more desirable procedure, more readily controlled and may be terminated at any time. The results seem to be as good as from a surgical enterostomy and an operative procedure (and sometimes two procedures, when secondary closure is required) is obviated.

3. Intubation served as a diagnostic aid in determining the site of obstruction. In this case this was not of great importance though from the evidence obtained the decision was made that further operative procedure would be unnecessary.

These cases have been selected for illustration because of the numerous complicating factors, thus demonstrating the widest range of application of intestinal intubation.



ship of the length of the suboccipitobregmatic diameter to the biparietal was essentially that that has been noted by other observers. In our series in the vertex cases the first named diameter was equal to or more than the second in 36 of the 43 cases. In the breech cases this relationship obtained in 3 of 3 cases, in the cesarean section cases 7 of 9, and in the cases measured from the fifth to the eighth day post partum in 15 of 15 cases.

The diagrams in Fig. 1 showing circumference outlines are representative tracings from the various groups named above. In these figures the dotted line represents a duplication of the bregmatic or broad half of the suboccipitobregmatic circumference.

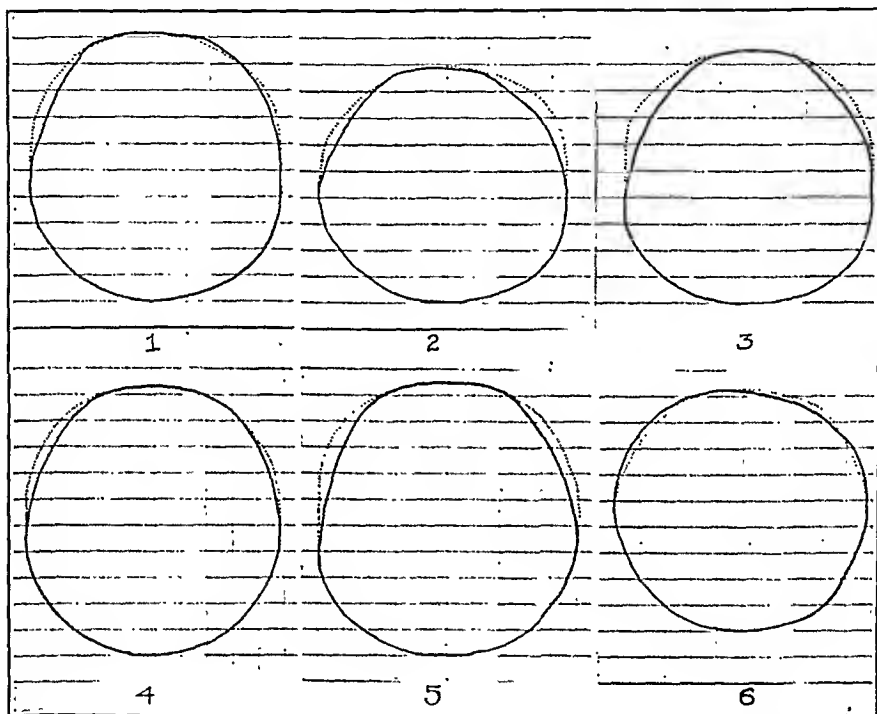


Fig. 1.—1, Represents the essential outline in 36 vertex cases in which the suboccipitobregmatic diameter was equal to or greater than the biparietal. 2, Represents the essential outline in 9 vertex cases in which the biparietal diameter was greater than the suboccipitobregmatic. 3, Represents the essential outline in the 3 breech cases. 4, Represents the essential outline in the 9 cases delivered at cesarean section. 5, Represents the essential outline in the 15 cases measured five to eight days post partum. 6, Represents the outline of the single case in which the configuration of the occipital half duplicated the bregmatic half of this circumference.

It is interesting to note that there is no difference in these contour relationships between the cesarean section series, in which no molding due to labor could have taken place, and the vertex cases, where such molding might have taken place. These findings are also confirmed in the 15 cases measured from the fifth to the eighth day of infant life when any effect of molding is said to be obliterated.

It seems clear from the findings mentioned that the suboccipitobregmatic circumference is not truly circular but ovate in shape with the bregmatic half definitely broader than the occipital half. This fact suggests an interesting speculation as to the role which such a shape may play in the process of internal anterior rotation in vertex presenta-

## THE SUBOCCIPITOBREGMATIC CIRCUMFERENCE\*

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FROM the standpoint of practical obstetrics obstetricians will agree that the most important of the various planes that bisect the fetal head is that outlined by the suboccipitobregmatic circumference. It is this part of the fetal head which is of such importance in studies having to do with cephalopelvic adaptation.

According to Beck<sup>1</sup> this section "is almost circular in shape and is the plane which passes through the pelvis in the normal mechanism of labor." Various figures are given for the biparietal and suboccipitobregmatic diameters which traverse this plane, and, in general, they are stated to average 9+ cm. and 9.50 cm., respectively. Riggs<sup>2</sup> figures for the white race are 9.25 and 9.70, and for the black race 9.05 and 9.29. Thus it will be seen that a plane with such unequal diameters cannot be a true circle.

Assuming that more knowledge concerning this plane might be of value in the study of cephalopelvic relationships, particularly in the mechanisms of labor, the authors have recently undertaken to evaluate certain aspects of this plane in the newborn. In order to obtain the contour of this plane in the living infant, we devised a pliable lead tape hinged in its center which permits the opening of the blades while each blade maintains its configuration. In obtaining the contour of the suboccipitobregmatic circumference, we place the hinged portion of the tape just below the occipital protuberance, with the child lying on its back and bring the blades across the parietal eminences to the posterior aspect of the anterior fontanel. The blades are then carefully opened and the lead tape removed from the child's head. The blades are then returned to their original position as they encircled the child's head, and tracing the outline on centimeter-squared paper becomes a relatively easy matter.

The material presented in this communication represents the results of this procedure in 70 infants born at term (2,500 gm. or over), 55 of which were measured within the first six hours following birth and 15 were measured from the fifth to the eighth day of infant life. In 43 instances of the first group, the birth followed a normal vertex presentation, in 3 the presentation was by the breech, and in 9 the child was delivered by elective cesarean section before labor.

The most interesting finding which was uniformly present in all cases, with a single exception, was that the contour of this circumference was found to be definitely ovate in shape, with the occipital half of the circumference narrowed and the bregmatic half broadened. The relation-

\*This study was made possible through the Research Funds of Yale University School of Medicine.

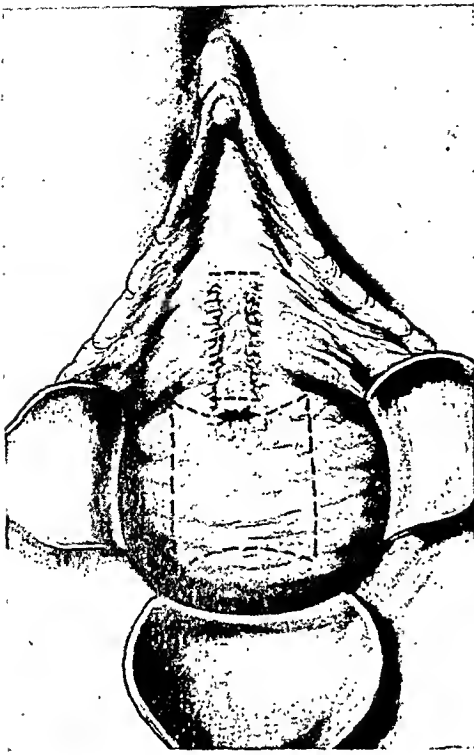


Fig. 1.

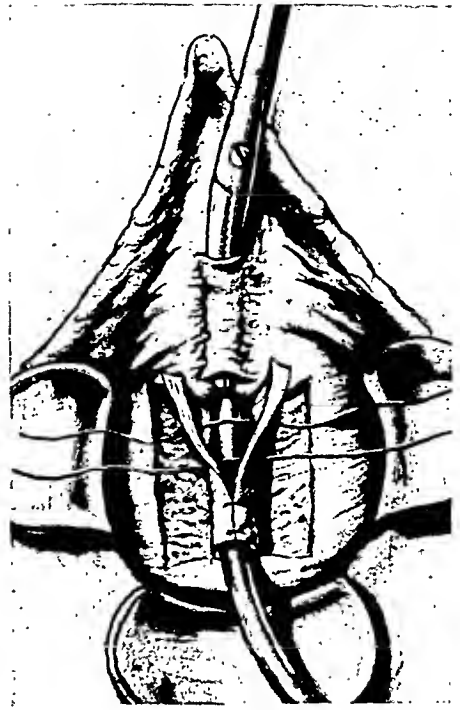


Fig. 2.

Fig. 1.—Shows the searred site of the previous urethra, and the fistulous opening. The dashed lines above the opening illustrate the position of the openings of the tunnel. Dashed line below the fistula is outlining the mucosal flap for tube.

Fig. 2.—The tunnel completed, the flap mobilized, the new urethral tube in the process of completion. Note the thickness of the flap in the proximity of the new urethrovesical junction.

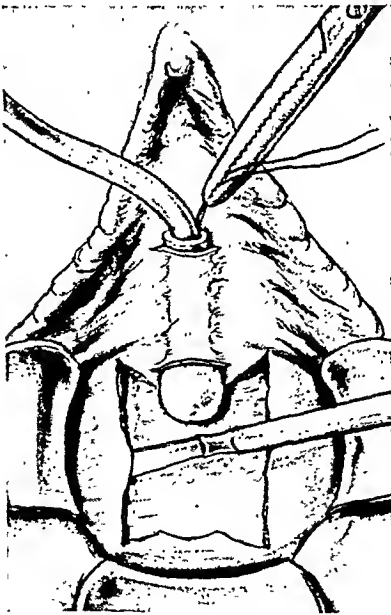


Fig. 3.

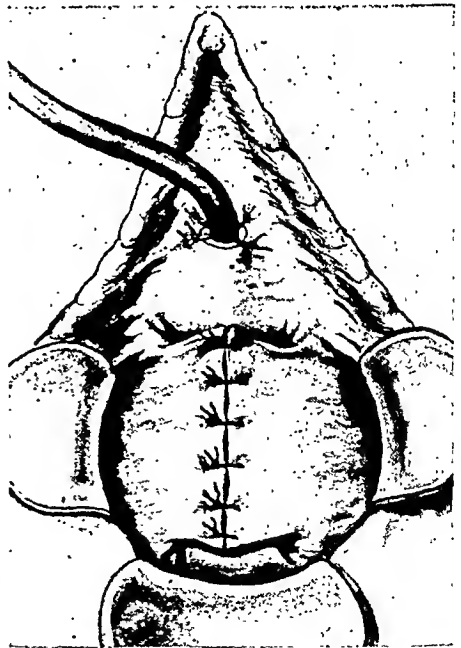


Fig. 4.

Fig. 3.—The new urethral tube drawn through the tunnel by means of traction sutures. The catheter which is passed through the new urethral tube into the bladder also drawn through the tunnel. The margin of the denuded mucosal flap undermined.

Fig. 4.—The complete operation, the new urethral tube anchored at the upper margin of the tunnel. The vaginal mucosa sutured covering the denuded area and bulbous end of the urethra. The catheter in place.

tions. We are reminded that the bony pelvic canal from inlet to outlet is definitely narrower in its anterior half, and that, in the adaptation of the flexed fetal head to this canal, anterior rotation of the occipital half of the suboccipitobregmatic plane would be the most favorable mechanical relationship.

We are not attempting at this time to explain anterior occipital internal rotation solely by the factors of mechanical adaptation, but it seems obvious that this movement is certainly favored by the shape of the suboccipitobregmatic circumference as we have found it.

#### SUMMARY

1. A device has been described which is useful in outlining fetal head circumferences, and by its employment the suboccipitobregmatic circumference has been outlined in 70 newborn infants.

2. This group represents infants born by different mechanisms, which includes vertex and breech presentation and cesarean section. In addition, 15 infants born following vertex presentation were measured on the fifth to eighth day of infant life.

3. In all instances but one, the suboccipitobregmatic circumference was ovate in shape with the occipital half narrowed and the bregmatic half broadened.

4. During the process of birth the mechanical advantage of anterior internal rotation of the occiput of the flexed fetal head is definitely favored by the shape of the suboccipitobregmatic circumference.

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## PLASTIC RECONSTRUCTION OF THE URETHRA\*

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COMPLETE destruction of the urethra following childbirth is not a frequent injury, but it has occurred sufficiently often to result in the development of various operative procedures to correct the deformity. Kelly, Farrar, Rawls, McGlynn, and Ward have described procedures whereby mucosal flaps were utilized to reconstruct the urethra. The greatest difficulty was the restitution of continence, and in most instances recourse was had to the use of varying types of pessary, which by external pressure in the region of the urethrovaginal junction gave at least partial control. In the case that I present a mucosal-lined canal was constructed and drawn through a tunnel. This procedure was successful in restoring a patent new urethra and maintaining absolute continence.

Mrs. A. C., aged 26 years, gravida i, para i, was delivered of a nine-pound still-born child three years previous to her entrance to the hospital. It was a difficult labor, instrumental in character, and following the delivery the patient noticed a urinary vaginal discharge.

On examination there was found an opening into the bladder situated about the level of the internal meatus (Fig. 1). There was no external meatus present and no evidence of urethra. The site of the urethra was replaced by a dense

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\*Read at a meeting of the New York Obstetrical Society, November 14, 1939.

## REGIONAL ILEITIS AS A PROBLEM IN PELVIC DIAGNOSIS\*

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REGIONAL ileitis is a granulomatous disease generally affecting the terminal ileum in young adults. In the stenotic type, a mass may be felt in the right lower quadrant of the abdomen. This mass of exudate and greatly thickened or adherent loops of gut may be felt on vaginal or rectal examination. If the cecum is involved in the necrotizing, granulomatous process, the mass is larger. It may be found so low in the right vaginal fornix, and so close to the uterus that it may easily be mistaken for an adnexal lesion. If, as may happen, there is no history of any unusual gastrointestinal disturbance or, if the patient has any complaint referable to adnexal disease, error in diagnosis may be made more readily.

The gynecologist confronted with the formidable pathology of regional ileitis should be able to cope with this lesion should he come upon it unexpectedly at operation. Better still, since intestinal resection and anastomosis are usually indicated, he should become familiar with its symptomatology and diagnostic criteria, so that he may not subject to laparotomy a patient with whom the general surgeon is better able to deal. Only recently identified as a disease, Crohn's<sup>1</sup> first paper appearing in 1932, regional ileitis is either actually increasing in frequency, or is being recognized more often. Its literature is already large, but up to now comprehensive reviews<sup>2-5</sup> pay scant attention to the fact that it may be confused with other pelvic lesions. Since the mass may appear to be of adnexal origin, it is obvious that recognition and perhaps treatment are of importance to the gynecologist.

Three times in two years, in our gynecological service, we have failed to make the diagnosis until the abdomen was opened, yet it is likely that in each case a diagnosis of regional ileitis might have been made, if we had but borne it in mind. Like ectopic pregnancy, a diagnosis is more often made if one but thinks of it. These three cases are reported in order to call the attention of gynecologists to this disease. Data of particular importance in differential diagnosis and surgical indications are quickly summarized.

### CASE REPORTS

CASE 1.—Mrs. S. N., para ii, gravida iii, was admitted to the Greenpoint Hospital Nov. 7, 1936, complaining of severe pain in the lower abdomen. There had been no nausea or vomiting. Similar attacks of pain, not so severe, had occurred at varying intervals for three years. Her menstrual period, one week ahead of time, had just

\*Read at a meeting of the Brooklyn Gynecological Society, December 1, 1939.

scar and some shaggy tissue, the remains of the urethral mucosa. It was decided because of the scarring that an attempt to utilize the original urethral site would be unwise, and it was planned to form a tube of vaginal mucosa and draw it through a tunnel approximately the site of the urethra. A transverse incision was made about  $1\frac{1}{2}$  cm. from the clitoris and the tissue undermined in the median line below the scarred surface, forming a tunnel for the new urethra. This terminated above the fistulous opening in the bladder (Fig. 2). A modified butterfly-shaped flap was outlined, with the bladder opening at the midpoint of the upper margin of the flap. The upper portion of the flap was intentionally made thicker than the lower to include, if possible, some sphincter fibers. This flap was 0.5 cm. longer than the tunnel that had just been made. The vaginal flap was dissected free, remaining attached only about the margin of the fistulous opening. The tube was then formed by suturing the mucosa with No. 1 chromic catgut. Traction sutures were introduced at the lower margin of the tube. A clamp was passed through the tunnel and the traction sutures grasped and drawn through the preformed tunnel (Fig. 3). The tube was then attached to the margin of the original transverse incision which represented the external meatus. The small catheter which had been introduced into the canal and bladder had also been drawn into the tunnel previously. The vaginal margins of the denuded area were undermined and united in the median line with interrupted No. 1 chromic sutures (Fig. 4). The patient's convalescence was uneventful, the catheter was removed on the sixteenth day. The patient now states that she is continent except during the convulsions of epileptic attacks which she has had since childhood. How continency was obtained in this case is difficult to explain. There is a possibility that the internal vesical sphincter was not damaged at the time of the original injury and that it functioned normally after the repair. On the other hand as will have been noticed in the previous illustrations (Fig. 2), the thickness of the flap at the margin about the internal meatus was much greater than at the other extremity of the tube, and the thick portion of the flap may have contained some muscular fibers of the bladder and of the sphincter. It is also possible that the cicatricial contraction of the tunnel about the tube aided in maintaining continence.

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#### DISCUSSION

DR. EDWARD A. BULLARD.—It seems to me that the doctor was a better surgeon than he realized; that he unwittingly sutured some of the sphincter fibers about the inner end of the urethra in closing the posterior segment of the wound. It is very important to suture these sphincter muscles firmly about the urethra and preferably throughout its entire length if we are to get complete control of urination.

DR. GEIST (closing).—Vaginal cystotomy was contemplated in this case, but because of the fixation of the bladder it was decided not to use that method of drainage. We have employed vaginal cystotomy, especially in recurrent fistulas and in urethrovaginal fistulas.

It is interesting to note how readily the cystotomy wound heals, quite in contrast to the persistence of an accidental injury.

stroma. The circular muscle showed edema and moderate lymphatic exudate, while the longitudinal muscle was relatively uninvolved. The serosa was thickened by round cell exudate, telangiectatic capillaries and venules and underlying ovoid calcified granules." The diagnosis was granuloma.

CASE 3.—R. M., a 16-year-old school girl, was admitted to the Kings County Hospital on April 4, 1939, complaining of persistent nausea, constipation, anuria, and sharp cramplike pain in the left lower abdomen. Beginning at eleven years of age, she had menstruated every two weeks for six or seven days each time. She had been sick for three months, had lost 30 pounds in weight, and reported discharge from another hospital where cystoscopy, intravenous pyelography, and a gastrointestinal series had been negative.

Temperature and pulse were normal. Hemoglobin was 78 per cent, leucocytes 9,800 with 72 per cent neutrophils. Abdominal examination showed tenderness in both lower quadrants and a mass to the right of the midline, three fingerbreadths above the pubis. The hymen was intact. Rectal examination showed a small conical cervix with pain on motion, and a retroverted uterus. To the right and anteriorly there was a firm, markedly sensitive mass about 10 or 11 cm. in diameter. The diagnosis was ovarian tumor and retroverted infantile uterus.

During the next few days she developed an acute pharyngitis, complained frequently of sharp abdominal pain and vomited occasionally. Temperature rose daily to 101° F. On April 12 the abdomen was opened under cyclopropane-ether anesthesia. A great mass of inflammatory tissue involving terminal ileum, appendix, and cecum was found, and the operating gynecologist called a surgeon who continued the operation. Huge glands in the ileocecal region of the mesentery were resected en bloc in Miculicz fashion, and the rent closed. The cecum and ascending colon were so mobile that the entire lesion could be held up about 25 cm. in a straight line above the abdominal wall. When the ileum and ascending colon had been paralleled with an atraumatic suture so as to produce a double barrel effect, the abdominal incision was closed and the lesion removed with the electrocautery knife. Immediate postoperative recovery was smooth. A spur crushing clamp was applied on the eighth day and removed four days later. Eight weeks after the primary operation a secondary closure of the colostomy was done. The patient then had regular bowel movements, and has made a good recovery. The diagnosis of regional ileitis was confirmed by the histology of the specimen. Since it resembled the pathologic report in Case 2, it is unnecessary to give it in detail.

A follow-up examination seven months postoperatively showed the patient to be in good health with a gain in weight of 35 pounds. A gastrointestinal series showed no evidence of recurrence.

#### DIAGNOSIS

Regional ileitis is a subacute or chronic disease of the ileum, principally the terminal ileum, but it may extend to the cecum and ascending colon or the upper ileum or jejunum. The destructive, ulcerating, cicatrizing, granulomatous process finally causes stenosis of the lumen of the intestine associated with a palpable lower abdominal mass and multiple fistulas, which are said to open commonly through an old laparotomy scar. It is seen most often in young adults. In women it generally occurs during the childbearing period, occasionally with acute onset. Usually, however, the history is one of insidious chronic illness, often with remissions lasting two to four weeks. The most constant symptoms are loss of weight, abdominal pain, and diarrhea associated with a palpable mass. The loss of weight is due to fear of eating, rather than the disease, since abdominal pain and cramps quickly follow ingestion of food. The pain is generally dull and cramplike, followed and relieved by defecation; it may be very sharp however and need not be confined to the right lower quadrant. Diarrhea is generally an outstand-

ended. Her temperature was 99.8° F., sedimentation time 80 minutes plus, and the blood count showed hemoglobin 81 per cent, red blood cells 3,450,000, white blood cells 10,000 with 84 per cent polymorphonuclears. Her abdomen was slightly distended and tender in the hypogastrium. On vaginal examination a large, elongated, rather cystic mass was found in the right fornix anterior to a retroverted uterus. The diagnosis was ovarian cyst or large hydrosalpinx.

At operation the tubes and ovaries were found to be normal and the uterus retroverted. About sixteen inches of terminal ileum in three adherent loops were found in the pelvis as a tumorlike mass. The intestine was dull red, thickened, and the mesentery pale and densely cicatrized. The cecum was distended and thin, and the appendix normal. The kinked loops were straightened by freeing adhesions, and the mesenteric scar was resected. Her immediate postoperative course was uneventful but recent examination shows a large abdominal mass and resection has been advised.

CASE 2.—Mrs. L. M., aged 39 years, was admitted to the Long Island College Hospital on Sept. 30, 1937, complaining of fatigue, occasional sharp pain in the right lower abdomen over an old laparotomy scar, dysmenorrhea and marked loss of weight. There were no gastrointestinal symptoms. She had been operated upon ten years before for intestinal obstruction which occurred one year after salpingostomy for sterility. For a week prior to admission she had noticed a swelling in the right lower abdomen. A tender, fixed, fluctuant mass about 9 cm. in diameter could be seen and felt beneath her old laparotomy scar. On vaginal examination there was no evidence of infection about the introitus, and the mass felt abdominally could be easily palpated in the right fornix with a well-marked sulcus separating it from an apparently normal uterus. The temperature was 101° F., leucocyte count 11,900 with 88 per cent neutrophils, and sedimentation time twenty minutes for 18 mm. The mass was thought to be adnexal in origin, adherent to the abdominal wall and infected. Incision drained about 2 ounces of foul pus yielding *B. coli* and enterococcus on culture, and she improved at once. On discharge, the right-sided mass was less tender and half its former size.

She was readmitted on Dec. 7, 1937, complaining of continuous discharge from a small opening at the site of the incision. A mass about 7 cm. in diameter was still present, and vaginally seemed to be a little higher. The sinus tract was injected with methylene blue, incised and packed, and she was discharged three weeks later with the wound almost healed.

On June 14, 1938, she was again admitted. The sinus had not healed, discharging continuously and at times profusely. For six weeks she had suffered epigastric pain, and had become emaciated. Indigo carmine granules by mouth did not appear in the wound drainage, nor did methylene blue injected into the sinus appear in the feces. The right-sided mass was still present. At operation, the abdomen was opened through an elliptical incision around the old scar. The pelvic viscera were normal. The fistulous tract was found to enter the terminal ileum which was markedly enlarged to a sausage-shaped, tumorlike mass. The cecum appeared normal. About 15 cm. of terminal ileum was resected, the stumps inverted, and transverse ileocolostomy performed with two cigarette drains in the right iliac fossa, and through-and-through closure of the abdomen. After a prolonged period of shock, she recovered completely and was discharged June 30, 1938, with the wound almost healed. It later healed completely. She had no complaints and gained 40 pounds in weight. She was readmitted during October, 1939, for incision and drainage of an abdominal wall abscess. The wound healed completely.

*Pathologic Report.*—(Dr. Benjamin M. Cissel.) "A lenticular segment of skin 7 by 2.5 cm. attached by dense bands to an underlying loop of small intestine 15 cm. long; on section its walls were thick and fibrous with heavy polypoidal mucosa. There were no enlarged lymph nodes in the attached omentum. Microscopic examination showed the mucosa largely destroyed and replaced by multiple miliary abscesses surrounded by zones of old infected granulation tissue; here the submucosa was invaded by an exudate of lymphocytes and plasma cells, largely perivascular. In other sections remote from the granulomatous area, the mucosa appeared to be normal, or moderately hyperplastic with moderate leucocytic infiltration of the



It may be surprising how it is possible for a lesion to keep developing in an intestine without symptoms, until suddenly, obstruction develops. To understand it, it is only necessary to recall the analogy of carcinoma of the descending colon where the disease can be present for six, eight, ten, or twelve months, as judged from the size of the growth, without producing any symptomatology, until with the onset of sudden edema from inflammation, closure of the intestinal tract occurs. Under such circumstances, the first sign may be symptoms of intestinal obstruction.

In the chronic phase, which is the one that is of interest to us, there are also two varieties: (1) As in the three instances reported tonight in which the disease was apparently progressing for a considerable period of time when general constitutional symptoms appeared, the most prominent being either diarrhea or loss of weight or a combination of those with anemia; and (2) the other variety which goes on to fistula formation, because ulcerations in the affected bowel, walled-off by neighboring viscera or by the abdominal wall, ultimately perforate into the viscus or on the abdominal surface.

In the chronic variety, difficulties may easily be avoided because in this type of case the gynecologist has ample time to make a complete study. In the acute variety, on the other hand, one has not that opportunity because, in the main, one must operate because of a mistaken diagnosis, such, for example, as appendicitis. We had 36 such cases and were able to make the diagnosis in only two. In reviewing the literature on the subject one finds that since 1932 over 200 articles have appeared, covering a total of 500 cases, and the diagnosis was almost never made in the acute variety.

Then the x-ray is an important aid, especially in the presence of a mass which can be felt abdominally. Even with a barium enema one can, in most instances, get filling of the terminal ileum and see the so-called string effect or string sign which was first described by Kantor. If there is any question about getting barium back into the ileum, plates taken at four, five, six, seven, or eight hours will invariably show the lesion. It is shown not only by the string sign, but also by irregularities in the terminal ileum, fixation of the wall and also loss of peristaltic motion in the involved portion of the bowel. The barium enema is very important, because the disease may be in the rectosigmoid and vaginal findings may appear in the left side of the pelvis.

Recurrences have been reported. It is a question in my mind whether these are recurrences or skipped lesions; that is to say, lesions that have been missed by the operator. In one case I got one man back three months after resection of a local lesion at the ileocecal junction and found that he had a recurrence in the small intestine, all the way up to the jejunum. The disease, in my experience, can go on for as long as seven years before the patient comes to operation.

Treatment of the chronic stage should, if possible, consist in eradication of the lesion by excision in one, two or more stages, depending upon the individual who is doing the operating and what his experience is with intestinal surgery. Wherever possible, it should be removed, and removed widely, because of the possibility of extension of the disease.

In this disease we will probably ultimately find some definite, specific cause. At the present time the only etiologic factor that has been offered has been developed through the work of Felsen. Felsen had the opportunity of examining cases of dysentery in New Jersey in the epidemic they had there. He was able to get 122 of them back into the hospital for study. He found that 46 patients had subsequent symptoms, and of those, 13 came to operation or autopsy. At operation, 10 showed chronic ulcerative colitis, 2 had regional ileitis at operation, and at autopsy 1 showed regional ileitis, an incidence of 3 cases out of the 122, which is much greater than occurs ordinarily in the general population.

Felsen claims that he can get specific agglutination for the dysentery in all these cases of regional ileitis. However, nobody has been able to corroborate his work. In our series, in only one case did we have a positive agglutination of 1:320. Felsen claims also he is able to isolate the bacillary dysentery organism, but no one is able to confirm that, despite careful work which has been done at the Mayo Clinic, Mount Sinai Hospital, and Beth-Israel Hospital.

ing symptom and occasionally there may be blood in the stool. Weakness, low grade fever, anemia, nausea and vomiting may be observed. Moderate leucocytosis may be present, and the sedimentation time accelerated. A mass, generally higher than that due to adnexal pathology, may be palpated in the right lower quadrant of the abdomen. The diagnosis can be made by x-ray. Since the cecum and colon are but rarely involved, the barium enema is usually negative, but the barium meal will show abnormalities in the terminal ileum. There may be distended proximal loops of bowel and a fluid level, as well as definite delay in motility. The characteristic findings are those of stricture of the distal ileum often with the "string sign."<sup>6</sup>

#### SUMMARY

X-ray would have established the diagnosis in all three cases. The intractable fistula, in one case, was typical of regional ileitis, yet that diagnosis did not occur to us, because the mass was pelvic. In the other cases a tumorlike mass was thought to be of adnexal origin, because it was deep in the pelvis. Chronic illness in a young woman, with weakness, loss of weight, dull abdominal or pelvic pain, cramps or diarrhea after eating, and a history of repeated remissions suggests regional ileitis. An abdominal mass to the right of the umbilicus or a fistulous opening near an old laparotomy scar is excellent confirmatory evidence. This mass may be mistaken for adnexal tumor, because of its proximity to the uterus or because of possible coincidental gynecologic symptoms. The x-ray will establish the diagnosis. Resection well beyond the involved area is indicated, for unless excision is radical the disease will spread. The two stage operation is the procedure of choice, as the mortality for primary anastomosis is high. Careful diagnostic study will protect the gynecologist who is not prepared to perform intestinal resection.

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#### DISCUSSION

DR. HARRY KOSTER.—My personal experience is concerned with 67 cases of this disease. I believe that the term "regional ileitis" is unsatisfactory because the disease is found in every part of the bowel, from the cardia down to the anus. Perhaps a better term would be chronic enteritis, nonspecific, cicatrizing and inflammatory; or chronic granulomatous inflammatory lesions of the intestine.

Crohn, Oppenheim and Ginzburg, in their paper in 1932, called the attention of the general medical public to this disease, but in 1913 T. K. Dalziel reported it under the term "chronic interstitial enteritis," mentioning that he had had an experience with 10 personal cases, 2 of them in physicians who had the disease throughout the whole gastrointestinal tract and who, needless to say, died.

In his other cases it was present in the ileum, jejunum, cecum, transverse colon, anus, rectum, and sigmoid. In our series of 67 cases we found a similar distribution to that of Dalziel, but in only one instance was the entire gastrointestinal tract involved from the duodenojejunal junction down to the anus.

cinoma, classification of the tumor according to Schmitz to determine operability, and the radiosensitivity of the tumor itself. The ability of the patient to withstand a major surgical procedure is of utmost importance. Obviously we must design our therapy primarily in the interest of the mother without regard to the fate of the fetus. Radium and deep x-ray therapy should be made the treatment of choice as in the nongravid state. It has long since been proved that this method gives better results than radical panhysterectomy as suggested by Wertheim, except in isolated instances when the growth must be very early, Class I, and the factor of pelvic infection ruled out. The tumor must also be well differentiated histologically. In all others, radium and deep x-ray therapy offers a distinct advantage.

The element of trauma to the diseased organ influences the type of delivery in those patients who are first seen late in pregnancy, or who progress to term despite treatment. We are greatly concerned with this type of case, because all observers are agreed that trauma to cervical carcinoma, incident to delivery from below, disseminates the malignant growth to a point where it is beyond help from any method of therapy yet devised. The most logical procedure then would be to treat the malignancy by radium and deep x-ray therapy without regard to the effect on the fetus, and deliver the child at subsequent cesarean section; this may be followed at a later date by an adequate amount of deep therapy. Mundell<sup>4</sup> presents evidence to prove that this form of treatment is attended by fair results even in respect to the fetus. He collected forty-two cases from the literature, treated with radium and x-ray during pregnancy with the following results: Twenty-one or 50 per cent had normal babies; eight or 19 per cent had abnormal babies; and thirteen or 31 per cent miscarried soon after beginning the treatment. The ideal situation is found when spontaneous abortion occurs early enough in the pregnancy to preclude the element of major traumatic injury to the affected cervix.

Cervical carcinoma in pregnancy does not differ from that found in nonpregnant females, except in its ultimate effect. The prognosis being graver, it behooves us to carefully consider each case as a distinct therapeutic problem.

To summarize, we find that the general opinion of those who have had contact with relatively large numbers of cases is that pregnancy exerts an unfavorable influence on the carcinoma for two reasons: Increased blood supply to the cervix and uterus, coupled with greater lymph drainage from the affected area; and the possibility of trauma and lacerations of the diseased cervix during labor. These things predispose to sepsis, hemorrhage, embolism, and metastasis. We are also certain that abortion is more common in the presence of carcinoma of the cervix, and is more likely to occur when the cancer invades the cervical canal. It is not certain, however, that this will occur; hence we may be faced with a decision to perform a cesarean section at term, regardless of the condition of the fetus at that time. There is evidence to support the fact that placenta previa occurs with greater frequency. Rupture of the uterine wall is a possibility when extensive carcinomatous invasion has taken place. As to labor, it is possible that a large carcinoma may inject an element of dystocia into the picture.

We can draw no definite conclusions from the case reports studied. There is great variation in the histology, classification, term of pregnancy, and methods of treatment; for this reason, we report the history, findings and therapy of a young primigravida, first seen when five months' pregnant, with a large polypoid mass attached by a broad pedicle to the left posterolateral wall of the cervix. This was determined to be malignant. Because of the nature of the lesion, it was felt that she had a better chance of cure by a radical panhysterectomy followed by deep x-ray therapy.

Mrs. C. F., married, negress, aged 32 years, was admitted to the Elizabeth Steel Magee Hospital, on Dec. 14, 1938. She had previously been seen for the first time on Dec. 12, 1938, in the Gynecological Out-Patient Department, complaining of vague pain in the left lower quadrant of several years' duration, at no time acute or disabling. In addition, for six months prior to admission she had noted vaginal bleeding for one to two days following intercourse; no other genitourinary symptoms could be elicited. Her past history was negative for serious illnesses, operations, or chronic familial disease. She began menstruating at 13 years, was always regular,

This is a very important subject for the gynecologist, not so much because he is likely to get into trouble at the operating table, but because in the differential diagnosis he has an opportunity of keeping in mind another disease which is coming to the forefront, in this country at least.

DR. ROSENTHAL (closing).—It has likewise been obvious that regional ileitis is not a satisfactory term. We merely desired to call attention to this disease as a problem for the attention of gynecologists.

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## CARCINOMA OF THE CERVIX IN CONJUNCTION WITH PREGNANCY\*

S. A. CHALFANT, M.D., AND J. H. MERING, M.D., PITTSBURGH, PA.

*(From the Elizabeth Steel Magee Hospital)*

IN A series of approximately 40,000 pregnancies at Elizabeth Steel Magee Hospital from 1921 to 1939, we found 3 cases of carcinoma of the cervix. This is an incidence of 0.0075 per cent and is a considerably lower figure than is usually quoted. While the incidence varies in the reports of many authors on the subject, all of them agree that pregnancy and carcinoma of the cervix together are rare. L. S. Emge<sup>3</sup> gives a comprehensive review of the literature up to that point. His own figures are 6 cases in 11,600 pregnancies, or 0.05 per cent. At the Kiel University Clinic, Gross collected statistics showing 120 cervical carcinomas in 224,080 pregnancies, or 0.053 per cent, practically the same figure obtained by Emge. De Lee<sup>6</sup> quotes 0.007 per cent in a large series, which more nearly matches the incidence at Magee Hospital. In 1935, Tagliaferro<sup>1</sup> in an extensive study reveals an incidence of 0.038 per cent. Danforth<sup>2</sup> in 1937 could find 3 cases in 20,444 pregnancies, or 0.014 per cent. Clinicians publishing figures on large series find one cervical carcinoma in 1,000 to 6,000 cases. De Lee and ourselves find one case in about 13,000 pregnancies.

It is generally thought that carcinoma of the cervix in a young woman is a more highly malignant process than that occurring in the higher age groups. The theory has been stated many times by well-known clinicians and pathologists that when it occurs in the second and third decades, we are dealing with a growth of greater relative malignancy due to an unknown biologic change or disturbed hormonal balance. Conversely, the growth does not progress so rapidly as a rule when seen in the fourth and fifth decades, and this is thought to be a result of better individual tissue resistance or a more even hormonal balance. These statements have no experimental proof as yet, but there is no doubt that in those women of the older age groups undergoing adequate treatment, there is a greater percentage of five to ten-year cures. It is interesting to note that in Emge's series of 6 cases, only one patient died in less than five years from the beginning of treatment. This was the youngest of the group, a 25-year-old para ii, gravida iii, with an inoperable squamous cell carcinoma, treated by radium. The remaining 5 patients were all alive five years later, two of whom had operable mature adenocarcinomas upon whom hysterectomies were performed, and 3 noncornifying squamous cell carcinomas, treated by radium. Nothing is proved by a small series such as this, but an 83 per cent average of five-year cures is very commendable.

We do not encounter this complication of pregnancy or vice versa very often, and it is shown by considerable study of the literature that no one clinician has had a large enough series of cases to state a definite plan of treatment. Under the circumstances, it is essential that we keep in mind several things based on each individual case; namely, the term of pregnancy, histologic character of the car-

\*Presented at a meeting of the Pittsburgh Obstetrical and Gynecological Society, October 9, 1939.

The patient was seen and examined in the Out-Patient Department on Feb. 9, 1939, and was found to be entirely symptom free. On Feb. 15, 1939, deep x-ray therapy was begun by Dr. S. M. Henderson. Using 140 K.V. and 25 M.A. through a 3 mm. aluminum filter, at 50 cm. target object distance, she was given seven treatments of 600 roentgen units each, direct to the vaginal vault. A total of 4,200 roentgen units were thus applied direct to the pelvis by the vaginal cone method over a period of one week. Beginning February 24, using 200 K.V., and 25 M.A. through 1 mm. copper and 1 mm. aluminum filter, she was given an average of five treatments weekly of 150 to 200 roentgen units through four portals around the pelvis, until 8,900 roentgen units had been applied to the pelvis externally. Treatment was discontinued on April 28, 1939. When seen on May 5, 1939, the patient was well, and without evidence of malignancy. Reaction to the operation and deep x-ray was negligible. There was moderate hyperemia and slight leucorrhea. Since then she has been seen at the Tumor Clinic at Magee Hospital on five occasions. Her course has been symptom free. Pelvic examination, Sept. 1, 1939, revealed a small ulcerated area in the vault of the vagina, not grossly suggestive of malignancy. On her last visit to this clinic, Sept. 29, 1939, this area was healed, but showed some induration, thought to be a result of scarring rather than a carcinomatous process.

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500 PENN AVENUE

## PREGNANCIES AFTER NEPHRECTOMY FOR TUBERCULOSIS

EDMUND LISSACK, B.Sc., M.D., CONCORDIA, Mo.

**P**REGNANCY sometimes occurs in women from whom a tuberculous kidney has been removed. Such a pregnancy may progress uneventfully but at the same time it should be borne in mind that the lone kidney may bear poorly the strain of a toxemia. Therefore the urine should be examined frequently, and the pregnancy interrupted at the first appearance of untoward symptoms. In the present case, in which a right nephrectomy was done for tuberculosis, I conducted the patient through four consecutive pregnancies, and successfully delivered four living and healthy children. Recovery in each instance was uneventful.

Mrs. M. R. F., aged 24 years, entered Research Hospital, Jan. 5, 1924, complaining of frequency of urination and pain in the right renal and ureteral region with daily rise of temperature.

After thorough and exhaustive laboratory examinations, including guinea pig inoculation, it was found that the condition was due to tuberculosis of the right kidney. Tubercle bacilli were isolated from the guinea pig.

On Jan. 7, 1924, Dr. E. G. Mark performed a right nephrectomy. The post-operative condition was good and the patient was released from the hospital in nine days. Two months afterward she married. Ninety-five days after the nephrectomy she presented herself for prenatal examination and care. Her last menstrual period was April 9, 1924.

At the time of the first prenatal visit, she complained of nausea and vomiting, slight faintness, and leucorrhea. Blood pressure was 110/70, temperature 98.6° F., pulse 84, urine showed a specific gravity of 1.020, acid reaction, clear, straw-colored, no albumin, no sugar, and no leucocytes.

Examination showed a well-nourished woman, weighing 185 pounds, heart and lungs normal, abdomen tense over the urinary bladder but otherwise normal. Pelvic

every twenty-seven to twenty-eight days, for three to five days. The last menstrual period was Nov. 23, 1938, apparently normal in all respects. During ten years of married life no contraceptives had been used and no pregnancies had occurred.

Examination on admission to the hospital revealed nothing of note in the general physical examination. Her blood pressure was 120/80; the urine was entirely negative; red blood count was 2.4, Hb. 42 per cent, white blood count 5,200, sedimentation time 24 min., nonprotein nitrogen 18 mg., blood sugar 91 mg., fasting; Wassermann reaction was negative.

Pelvic examination showed a marital introitus with a nulliparous outlet. There was no demonstrable infection of Skene's or Bartholin's glands; the urethra and vagina were negative. On visualization of the cervix, a cauliflower-like, extremely friable mass was seen protruding from, and attached to the left posterior aspect of the cervical lip by a broad pedicle. This mass was about 3 cm. in diameter and bled profusely on the slightest manipulation. A small portion was removed for pathologic section and diagnosis. The uterus was enlarged to the size of a five months' pregnancy, but could not be well outlined, due to the mass in the vaginal vault. No masses were felt in the adnexa. Tamponade of the vagina was necessary to control hemorrhage from the cervical growth. On Dec. 17, 1938, the patient was given a gas-ether anesthesia preceded by a small rectal installation of avertin. The pedicle of the cervical growth was doubly clamped and the mass severed from the cervix, the clamps being left in place to control hemorrhage. This material was also sent to the laboratory for pathologic examination. While she was anesthetized, the uterus was felt to be symmetrically enlarged to the size of a five months' pregnancy, soft and mobile. The cervix, visualized for the first time was bluish in color, and Hegar's sign was positive. A flat plate of the abdomen was taken the same day, and showed a fetal skeleton in utero.

On Dec. 19, 1938, she was given 500 c.c. of whole blood (Soresi). On the same date the original biopsy was examined microscopically and found to be a noncornifying, squamous cell carcinoma of the cervix.

*Pathologist's Report:* Dr. Mortimer Cohen: "The section consisted of actively growing tumor cells which invaded the cervix musculature in dense columns and sheets. The cells had a somewhat elongated spindle shape and were very hyperchromic. Many mitotic figures were seen. Some of the cells showed a pavement cell arrangement while others presented an alveolar type of structure. Throughout the myocervium were dense numbers of inflammatory cells including lymphocytes, plasma cells and polys."

*Diagnosis:* Squamous cell carcinoma of the cervix: noncornifying type.

Another transfusion of 300 c.c. of whole blood was given on Dec. 27, 1938, and on the following day her blood count was as follows: red blood count 3.4, Hb. 55 per cent. All phases of her blood chemistry were normal. The patient was prepared for operation on Dec. 31, 1938, and a cautery circumcision of the cervix was performed followed by a panhysterectomy. At operation only a small area of induration in the left posterior wall of the cervix was seen and no evidence of parametrial involvement could be found. No glands were palpable in the hypogastric or lumbar chains. The tubes and ovaries were normal in the gross. The uterus contained a female fetus of 570 Gm., with a normally implanted placenta. A portion of the omentum was adherent to the left adnexa. To the fimbriated extremity of the left tube was attached a 4 by 6 cm. thin-walled unilocular cyst, containing a clear watery fluid.

The patient had an uneventful postoperative course, the highest recorded temperature being 100.4° F. There was slight nausea and vomiting for three days, but no abdominal distention or chest signs. The wound healed by primary union. She was discharged eighteen days later on Jan. 18, 1939, without complaints, in good general condition with a red blood count of 3.4, and a Hb. of 60 per cent. Careful instructions were given for the patient to return for deep x-ray therapy four weeks later.

*Final report:* (1) Noncornifying squamous cell carcinoma of the cervix, (2) chronic endocervicitis, (3) five months' gravid uterus, (4) female fetus and placenta, (5) left parovarian cyst, (6) corpus luteum verum, and (7) follicular cysts and corpora albicantia of the ovary.

Over three years later, Aug. 19, 1938, Dr. W. G. Thompson and I had the privilege of doing a fluoroscopic examination of the chest and abdomen. Dr. Thompson's report follows: "The chest shows a normal cardiac silhouette. In the hilar region of the right lung there is found a moderately sized fibrocalcic gland probably of a tuberculous nature. The left lung has one or two such small calcific areas also. The oral barium meal observed fluoroscopically shows a normal esophagus. The meal enters a stomach of medium size, water trap type, with slow peristalsis. There are no ulcer defects on either curvature. The stomach is markedly ptotic, lying low in the pelvic vault. The pylorus is free from spasm or obstruction and the duodenal cap is visualized, normal and freely movable. The stomach empties slowly, the delay being due to poor muscular tone and not to any obstructive lesion. An x-ray film made of the stomach confirms the fluoroscopic findings."



Fig. 1.—X-ray of the abdomen. Note the outline of the ptotic stomach and also the calcified mesenteric gland. The left kidney outline is faintly seen at the upper right hand corner of the plate.

On Nov. 7, 1938, an x-ray of the chest and abdomen was made and showed the following findings. Quoting Dr. Thompson: "In addition to confirming the previous fluoroscopic findings we may add that the bilateral fibrocalcic nodules may probably be of a tuberculous nature but they do not appear to be active now. We do not see any active tuberculosis in the left kidney. There is no evidence of calculi in the left kidney which, however, is somewhat enlarged, no doubt a compensatory hypertrophy. The opaque bodies in the right upper abdomen are evidently old calcified mesenteric glands and are probably of no consequence."

#### SUMMARY

Despite a nephrectomy for tuberculosis, this patient was successfully delivered of four living and healthy children. It would appear that, generally speaking, nephrectomy is not a contraindication to pregnancy.

measurements: Interspinous 24 cm., intercrystal 25 cm., intertrochanteric 33 cm., external conjugate 20 cm., transverse diameter of outlet 11 cm., diagonal conjugate 12.5 cm.

The patient returned for 17 prenatal observations during this first pregnancy. The urine examinations at all times were negative, except on Dec. 10, 1924, when she complained of swelling of the legs, feet, arms and hands, dizziness and headache, and the urine contained a slight trace of albumin.

She was advised about her condition, told to be watchful for symptoms of eclampsia and instructed as to her care. Rest in bed was prescribed, with limited fluid intake, increased elimination, and salt-free diet. Clear and distinct fetal heart tones, rate 120, were heard to the right of the umbilicus. Blood pressure was 120/80. Right occipitoposterior position was diagnosed.

Labor pains commenced about 2 A.M. Jan. 17, 1925. Membranes ruptured spontaneously at 11 A.M. The cervix was fully dilated at 1 P.M. The head was on the perineum, and the patient was having strong pains and making good progress. A female infant, weighing 7½ pounds, was delivered at 1:30 P.M. Two tight loops of cord around the neck were freed and resuscitation successfully applied. Chloroform anesthesia was used.

The placenta was expressed about forty minutes after the delivery and 1 c.c. of aseptic ergot was administered. A second degree laceration occurred which was immediately repaired.

Patient rested in bed for ten days. The baby was nursed at the breast.

Postnatal examination at five weeks post partum revealed a normal condition, perineum well healed, introitus fairly roomy, cervix smooth and closed, uterus in anterior position, freely movable, and well involuted. Urine clear, amber in color, sp. gr. 1.020, no sugar, or albumin. Patient weighed 200 pounds, a gain of 15 pounds over prepregnancy weight.

July 14, 1927, patient returned for maternity care for the second time. Physical examination at this time was negative, excepting that the teeth needed attention. Urine was cloudy, gray in color, sp. gr. 1.015, alkaline, no albumin, or sugar. Sediment, causing turbidity, was composed of urates and phosphates.

July 16, 1927, Mosenthal test, from urine taken from 10 A.M. to 8 P.M., showed a specific gravity varying from 1.009 to 1.020. Night urine, sp. gr. 1.025. Urine showed a trace of albumin, was cloudy, contained no sugar, but did have quite a sediment, with few pus cells and hyalin casts. Mosenthal tests were repeated several times with specific gravities varying from 1.010 to 1.020. Albumin and casts were never abundant.

Patient was placed on low protein and salt-free diet and rest in bed. Bromides were prescribed. Condition responded readily. Blood pressure 125/80. This second pregnancy was marked only by much nausea and vomiting in the early months.

On July 19, 1927, urine showed a very slight trace of albumin with 2 to 4 white cells to the high power field. There were no red cells and no casts. Her output of dye (phenolsulphonphthalein) was 53 per cent with a two-hour period, during which time she put out 585 c.c. of urine. Her intake for the twenty-four hours was 52 ounces and her output 50 ounces. Nonprotein nitrogen was 28.6; creatinin 1.7; sugar 84.7, all well within the normal limit. Nothing was found in her blood count to indicate any infection, her hemoglobin being 82 per cent with 4,540,000 red blood count and 7800 white blood count.

Patient reported for 14 prenatal observations during this second pregnancy. Several Mosenthal tests were made, all showing a variation in specific gravity from 1.004 to 1.010.

On March 15, 1928, the second baby was born; labor and puerperium were normal. Thereafter, this patient went through two more pregnancies normally. The third baby was born March 17, 1932; the fourth, Aug. 21, 1934.

Patient visited the office April 17, 1935, for a postnatal examination. At this time the urine was straw colored, sp. gr. 1.020, clear, albumin and sugar free. Blood pressure was 120/80, Hg 90 per cent. Patient, who lives on a farm, has been doing all of her own house work and even milking. A Mosenthal test, from urine the day after this examination, 24-hour specimen, showed a specific gravity varying from 1.010 to 1.022.



The patient was admitted to the Hospital for Joint Diseases on Jan. 28, 1939. Laboratory findings were as follows: Urine was normal; basal metabolism, -10; specific dynamic action of proteins, -3; Wassermann and Kahn tests, negative; hemoglobin, 14.6 per 100 c.c.; erythrocytes, 4,960,000; leucocytes, 10,700; segmented neutrophils, 53 per cent; lymphocytes, 47 per cent; sedimentation, 6 mm.; blood sugar, 109 mg. for 100 c.c.

Roentgenograms gave no evidence of enlargement of the sella turcica, skeletal abnormalities, or metastases.

*Operation.*—On January 29, a preliminary dilatation and curettage was done. After entering the abdominal cavity, difficulty was encountered in delivering the tumor, due to adhesions from the previous operation. The tumor of the left ovary was of about the expected size, had a smooth surface, felt elastic, and resembled a large cyst. Adherent to the tumor was an atrophic tube. The right ovary was of normal size, with a whitish corrugated surface, and the right tube was normal.

A left salpingo-oophorectomy was performed in the usual manner. Both adrenal glands appeared to be normal on palpation.

Convalescence was uneventful. The patient was discharged on the thirteenth postoperative day. On the twelfth day her voice began to resume its normal pitch.

Menstruation occurred on Feb. 20, 1939, twenty-six days after operation, and lasted five days. This was the patient's first period since November, 1936. It has since recurred at regular intervals of about four weeks, with a moderate flow lasting four to five days. The breasts have filled out and returned to their original size. The hair on the upper lip has practically disappeared, and that on the extremities has become very scanty. The clitoris is smaller than before the operation, now measuring  $3\frac{1}{2}$  cm., but is still above normal size.

Pelvic examinations at intervals of three and six months, respectively, after operation have shown no evidence of recurrence. The patient is now in perfect health and enjoying her marital life.

*Pathologic Examination.*—(Dr. L. Motyloff.) *Gross:* The specimen consisted of an ovarian tumor, somewhat heart-shaped in contour and flattened anteroposteriorly. It measured approximately 10 by 9 by 4 cm. The capsule was intact and presented some purplish hemorrhagic areas. Section revealed the escape of a considerable quantity of bloody fluid from numerous cystic spaces, which honeycombed the specimen. The lining of the cysts was smooth. The intervening tissue was soft, somewhat edematous, and homogeneous. It was of pale yellowish brown color.

*Microscopic:* The tumor presented in some areas groups and sheets of cells scattered through fibrous connective tissue, without any regular arrangement and somewhat imitating the "whorls" of the ovarian stroma. In other areas distinct cords were formed, in dense arrangement, with very scant stroma between them (Fig. 1). The cell cords were running parallel or bending upon each other, and consisted in some areas of two layers of cells only, with the nuclei of the cells placed at a right angle to the long axis of the cords. A zigzag arrangement of the cords could be noted in some instances. Distinctly formed tubules were missing, but attempts at formation of tubules could be assumed here and there. The individual tumor cells were oblong, almost spindle-shaped, with a fairly large, deeply stained, rounded nucleus, occupying the greater part of the cell.

The stroma of the tumor was scant, oligocellular, and rather vascular. The blood vessels were almost exclusively of capillary character. In other areas the stroma was more abundant, and the tumor cells filled out the spaces between the individual stroma bundles, following the direction of the latter. (Low histolytic properties of the tumor cells?)

A rhythmical, palisade-like arrangement of the tumor cells could be encountered in some areas (Fig. 2). This arrangement was more typical of tumors of the connective-tissue order, such as myoma and sarcoma, than of epithelial neoplasms. The numerous cysts which were honeycombing the tumor (on gross inspection) were lined with a single layer of flattened cuboidal cells. The tumor cells did not reach the lining of the cysts.

The central mass of the tumor cells was surrounded by a zone of rather edematous, loose vascular connective tissue, with inclusions of fairly large groups of cells of epithelioid appearance (Fig. 3). Their cytoplasm was abundant, foamy,

Patients showing no abnormalities may be allowed to continue pregnancy under close observation.

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1009 MAIN STREET

## MASCULINIZING TUMOR OF THE OVARY (ARRHENOBLASTOMA)\*

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(From the Department of Gynecology, Hospital for Joint Diseases)

MRS. H. O., a white married woman, aged 28 years, was first seen on Jan. 18, 1939. Her chief complaint was sterility, with amenorrhea since November, 1936. Family history was negative; four sisters are living and have children. There were no known endocrine disorders or mental abnormalities in her family.

Menstruation began at fifteen years, was of three to four days' duration, and occurred at regular four-week intervals up to the age of nineteen. Patient was married in 1929, but had never been pregnant. In December, 1931, she had menorrhagia for eighteen days, and again in January, 1932 for twelve days. Following this, a dilatation, curettage, and a Gilliam suspension operation for retroflexed uterus were performed on Feb. 3, 1932. Thereafter, menses were regular until November, 1936, when they suddenly ceased.

The patient had always had good health, but during the past two years she had noticed an increasing growth of hair on her upper lip and chin, and a still heavier growth on her arms and legs. Since March, 1937 she and her family had noticed that her voice was getting hoarse and low pitched. This was diagnosed as chronic laryngitis. In the last two years she had lost 28 pounds.

Since August, 1938 there had been occasional sharp pain in the left lower quadrant, accompanied by backache. Her libido had decreased markedly, and her husband had noticed a striking enlargement of the clitoris.

Physical examination showed the patient's height to be 5 feet 5 inches, and weight 148 pounds, in contrast to 170 pounds in 1936. Her form was rather masculine and angular, with flattened breasts, a growth of fine hair on upper lip and chin, and an increase of hair on the arms and legs. The pubic hair was feminine in type. Blood pressure was 110/85.

Pelvic examination disclosed a marital outlet without relaxation. The external genitalia were normal except for a definite enlargement of the clitoris, which measured  $4\frac{1}{2}$  cm. in length, with a much thickened body, and a glans about one-half centimeter in diameter. The uterus was of normal size and pushed to the right. Below and behind the uterus was a mass about the size of a grapefruit, of cystic consistency, and situated deep in the Douglas pouch. This was evidently a tumor of the left ovary. The right adnexa were not palpable.

In view of the defeminizing and masculinizing symptoms associated with a palpable tumor, a diagnosis of arrhenoblastoma was made.

\*Presented at a meeting of the Section of Obstetrics and Gynecology, New York Academy of Medicine, November 28, 1939, and at the Twelfth Annual Graduate Fortnight, New York, October 23 to November 3, 1939.

and stained pink with sudan. Their nuclei were round, almost vascular. These cells closely resembled the interstitial cells of the hilum of the ovary. They differed from the oblong cells of the tumor proper, which had a scant cytoplasm with a relatively large nucleus. They did not stain with sudan.

A few primordial follicles were found in the edematous outer zone of the specimen (Fig. 4). Only a slight proliferation of the follicle cells could be noted. Mature and Graafian follicles were missing entirely.

*Diagnosis.*—Arrhenoblastoma of the intermediate, undifferentiated type.

The curettings removed at the time of operation were diagnosed as atrophic endometrium. The microscopic sections revealed fragments of cervical epithelium and a few shreds of endometrium containing small resting endometrial glands.

An endometrial biopsy taken on March 31, two months postoperative, was reported as follows:

Gross specimen showed about 0.5 c.c. of small endometrial fragments. Microscopically, the fragments were seen to consist of rather delicate, vascular (typical) cytogenic stroma and functioning endometrial glands. The latter were not very numerous. The degree of function corresponded to the end of the third week of the twenty-eight-day cycle. Diagnosis (by Dr. L. Motyloff): Endometrium in the early secretory phase. This indicates a resumption of the normal menstrual cycle after extirpation of the neoplasm, in comparison with the amenorrhea and atrophic endometrium before the operation.

Sections of the tumor were submitted for opinion to Dr. Emil Novak, of Johns Hopkins Hospital, Baltimore, and to Drs. Henry Jaffe, Louis Lichtenstein, and Alfred Plaut of New York, and I wish to thank them sincerely for their kind cooperation.

#### HORMONE STUDIES

At the present stage of our knowledge of blood and urine hormone studies, the question arises whether such investigations have any value in the diagnosis of arrhenoblastoma. When we bear in mind that male and female sex hormones are found in the urine of both sexes, not much help can be expected.

In this case, the examination for male sex hormones, made by Dr. R. A. Bosee after the operation, showed only one-tenth of the amount usually found in the urine of a male. The determination of male sex hormones made before the operation gave indefinite results, possibly due to the scant quantity of urine available for examination. The quantity of female sex hormones, determined by Dr. Motyloff in the laboratory of the Woman's Hospital before the operation, was diminished, and this diminution persisted for two months after operation. No increase of prolan could be noted before the operation.

#### SUMMARY AND CONCLUSIONS

1. A case of arrhenoblastoma of an undifferentiated, intermediate type has been presented.
2. The clinical features of masculinization and defeminization, associated with the finding of a palpable pelvic tumor, justified the diagnosis of arrhenoblastoma.
3. It is generally agreed that these tumors arise from embryonic rests in the ovarian hilum differentiating along male lines.
4. The assays of both sex hormones are of little help in diagnosing arrhenoblastoma, and further investigation is necessary for enlightenment as to their significance.
5. Additional studies may throw light on the question: Why do some tumors in this group masculinize the patient, while others do not? The subject merits investigation.

In conclusion, I wish to thank Dr. Howard E. Lindeman for his valuable assistance and advice in preparing this paper. And I wish also to offer my sincere thanks to Dr. Motyloff for his painstaking pathological studies, which enabled me to arrive at the final diagnosis; and to Dr. Nokamura for his technical assistance in preparing the slides and photomicrographs.

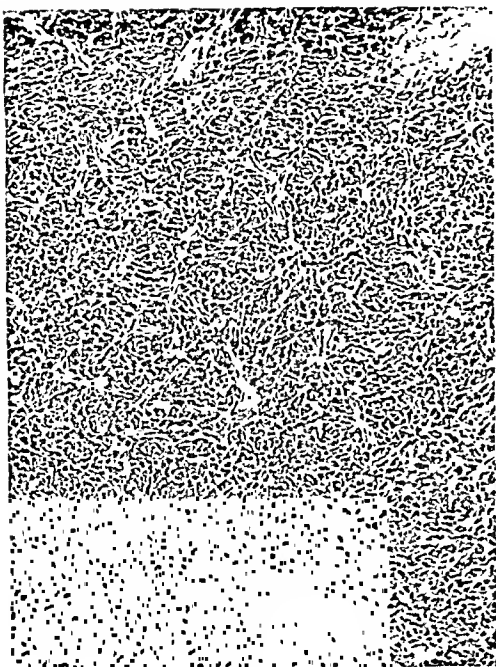


Fig. 1.

Fig. 1.—Showing tumor cells arranged in solid cords imitating tubules. (Note the scant stroma.)

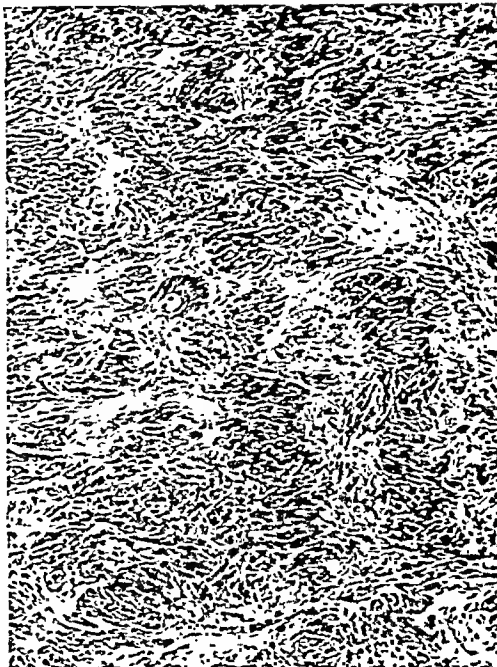


Fig. 2.

Fig. 2.—Rhythmical (palisade-like) arrangement of tumor cells (more typical of connective tissue tumors).



Fig. 3.

Fig. 3.—Interstitial cells in large groups (in the edematous zone of the periphery of the tumor).

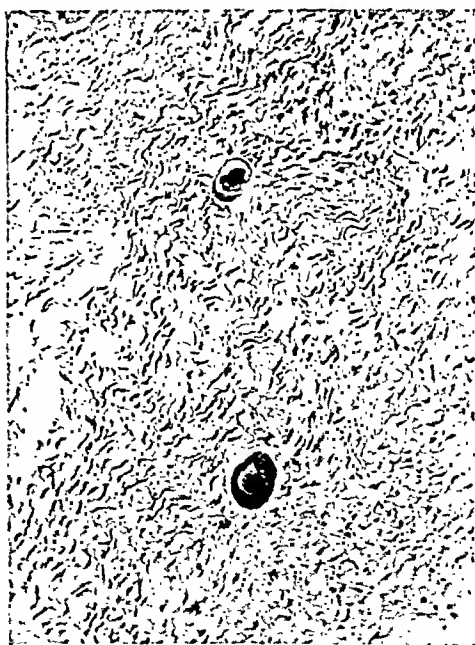


Fig. 4.

Fig. 4.—Primordial follicles in the outer edematous zone of the tumor (note the premature degeneration of the primordial follicles).

was a well-circumscribed, tender, firm mass about the size of a small orange. The left-sided mass was multinodular, firm, not tender, and the size of a small grapefruit. The fundus was intimately attached to these bilateral masses; it did not feel enlarged and was anterior in position.

The preoperative opinion was that of ovarian tumors. Krukenberg tumors were suspected because of the long-standing gastrointestinal symptoms, ascites, and bilateral involvement. Papillary cystadenoma or cystadenocarcinoma, however, could not be ruled out.

Laparotomy was performed on Sept. 24, 1937, under nitrous-oxide-ether anesthesia.

The peritoneum was entered through a lower midabdominal incision. About 1.5 gallons of clear straw-colored fluid were aspirated from the peritoneal cavity. The parietal peritoneum was studded with grayish nodules each about 2 mm. in diameter. The uterus was slightly enlarged, anterior, symmetrical, and smooth, except on the lower anterior surface which was covered with nodules similar to those found on the parietal peritoneum. These nodules were also found scattered over the broad ligaments. Each ovary was the size of an orange, irregularly ovoid

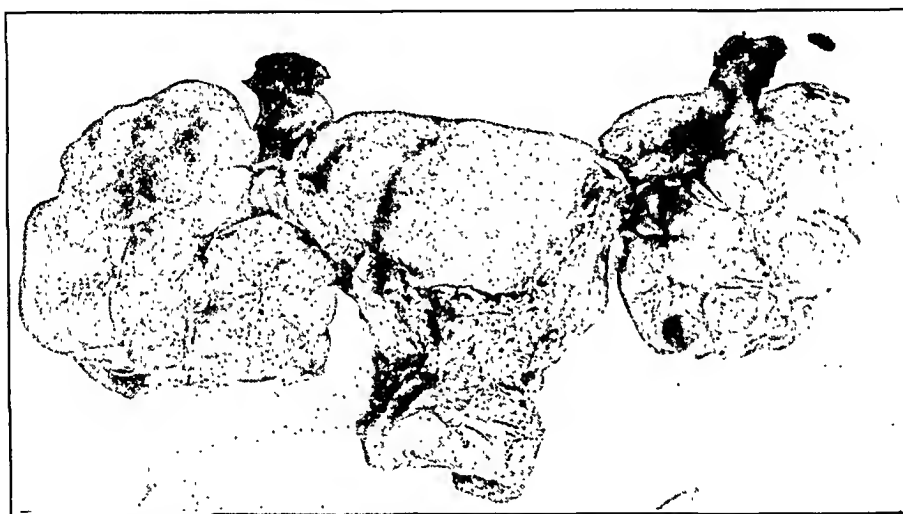


Fig. 1.—Uterus, with cervix, both tubes, and ovaries, showing enlarged and bosselated ovaries. There is no gross evidence of involvement of the rest of the adnexa, although the course and shape of the latter are distorted by dense fibrous adhesions.

and solid in consistency. The tubes were thickened and congested, with some areas of induration. The appendix was congested, thick and also had gray indurated areas. The liver, gall bladder, and stomach disclosed no gross pathologic changes on palpation.

The operative procedure consisted of a total hysterectomy, bilateral salpingo-oophorectomy and appendectomy.

*Macroscopic Examination.*—Specimen consisted of a uterus and adnexa, accompanied by an appendix and portions of broad ligament.

The uterus measured 6 by 7 by 5 cm. The cervical lips were stellate and edematous and presented several cysts. There was also an erosion of the cervical mucosa, and the canal was reduced to a very narrow channel. The endometrial cavity was also reduced in size to 5 by 8 by 3 mm. The myometrium was about 4 cm. thick.

The tubes were each about 8 cm. in length, tortuous, and presented numerous folds due to tuboovarian adhesions. The fimbriated end of the right tube was extremely hemorrhagic and edematous.

The right and left ovaries measured, respectively, 8 and 10 cm., in greatest diameter. The organs were multilobulated and presented yellow gray and blue mottling of their surfaces. Cystic portions of the organs were demonstrable through the capsule. On section the tissue was found to consist of portions of dense, gray, as

## KRUKENBERG TUMOR WITH INVOLVEMENT OF THE APPENDIX

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IN ONE of the many excellent papers on the subject of Krukenberg tumors, one author, Andrews<sup>1</sup> offered as a reason for publishing his three cases the fact that it was an "attempt to contribute some small bit of material for the study of a rare and fatal disease." It is with the same hope of contributing a bit more, that the present interesting case is submitted for publication. No attempt is made here to review the literature on the subject of Krukenberg tumor. In the last twenty-five years this has been done most admirably by Stone,<sup>2</sup> Major,<sup>3</sup> Fallas,<sup>4</sup> Hundley,<sup>5</sup> and more recently by Jareho,<sup>6</sup> to cite but a few of the more prominent writers. It is interesting to note, however, as Jareho points out, that out of the total of 303 cases which have been collected to date, nearly two-thirds of the entire number were reported since 1934. Despite the recent re-awakening of interest in the study of this malady, the origin of the tumor and its mode of spread are still among its controversial aspects. Thus, although it has been quite definitely established that the type of ovarian tumor originally described by Krukenberg<sup>7</sup> in 1896 is usually not primary but is secondary to carcinoma elsewhere (stomach, small intestines, colon, gall bladder, pancreas, breast, and even adrenal), it has not yet been entirely disproved that the same type of neoplasm could in some instances also be ovarian in origin. It becomes quite obvious that a much larger collection of cases than is at present available for study is necessary in order to arrive at more accurate conclusions regarding some of the disputed points. With that purpose in mind the following case is reported:

Mrs. J. R., a Russian Jewess, 50 years of age, housewife, was admitted to the Prospect Heights Hospital on Sept. 22, 1937, complaining of nausea and swelling of the abdomen. Her family history was essentially negative.

She had been married twenty-seven years. Her husband was living and in good health. She had a tonsillectomy performed in 1925. Menstruation started at the age of 15, recurred regularly about every twenty-eight days, was of five days' duration, and was not associated with pain or clots. Her last menstrual period occurred on Sept. 4, 1937.

She had had four full-term pregnancies, all terminating by spontaneous delivery. Three children were living and well. The oldest was 27 and the youngest 18. One child died of pneumonia at the age of 15 months. There had been several miscarriages of two to three months' gestation, the last one having occurred more than ten years ago.

Her complaint on admission dated back eighteen months, when nausea first appeared and continued intermittently with occasional vomiting. There had never been any pain associated with it. Abdominal enlargement was noted for one week prior to admission to the hospital. Her bowels were regular and there were no urinary symptoms. There had been some loss of weight prior to hospitalization, but the exact amount was not known.

On physical examination one noted a highly nervous, emaciated female weighing 117 pounds. The heart and lungs were normal. The blood pressure was 160/100.

The abdomen presented a uniform rounded enlargement which was soft and tender. A hard mass could be felt in the lower left quadrant extending to four fingerbreadths above the symphysis. There was dullness in the flanks and a fluid wave could be elicited. Pelvic examination showed a parous introitus with a firm pelvic floor. The cervix in the axis of the vagina was firm, eroded, cystic, closed, and insensitive. There were hard masses in both fornices. The one on the right

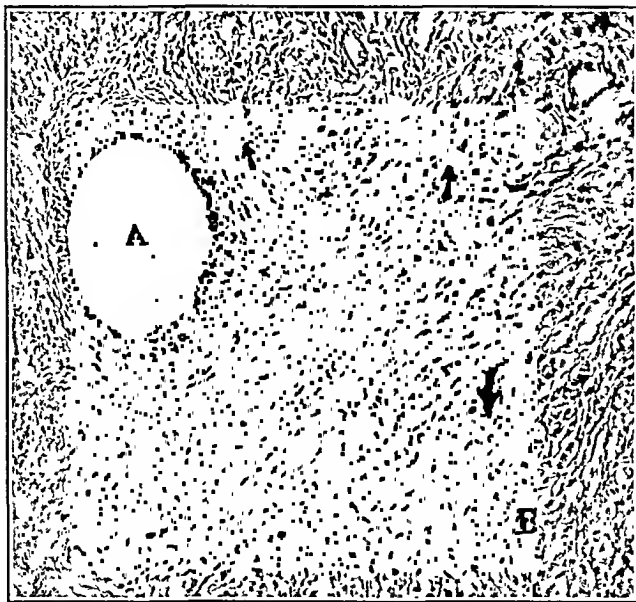


Fig. 2.—A high power magnification ( $\times 220$ ) of a representative section of the ovarian mass, showing a follicle (A) and ovarian stroma (B), characteristically infiltrated with Krukenberg cells. Arrow points to typical mucoid, signet ring, epithelial-like cells in the stroma which in some areas (large arrow) assume a myxomatous character.



Fig. 3.—A high power magnification ( $\times 200$ ) of a cross section of the Fallopian tube. The arrows point to nests of mucoid, epithelial cells lying in lymph capillaries of mucosal rugae (A), subepithelial layer (B), and muscularis (C). Arrow at D points to clusters of similar cells found in the interstices of the stroma.

well as hemorrhagic structures interposed between small cystic areas, some of which contained fluid blood. The cut surface of the right ovary showed a hemorrhagic corpus luteum in the midportion of a dense, solid, gray granular structure, extending to the periphery of the organ.

The portion of broad ligament was about 3 mm. thick, and on section presented a nodular cut surface of yellow gray tissue.

The appendix was 5 cm. long. The surface was red and rough. The wall was irregularly thickened. The contents consisted of blood and mucus. The mucosa was intensely red and rough. The mesoappendix was considerably thickened by a yellow granular structure.

*Microscopic Examination.*—The uterine endometrium presented interstitial hyperplasia. The myometrium showed separation of some of the interlacing bundles of muscle by distended lymphatics and blood vessels, about which were scattered a number of large, deeply pink-staining cells with small nuclei, some of which were vesicular. In some sections these cells displayed a tendency to colloid accumulation in the cytoplasm and simulated closely the neoplastic cells to be described below in the "ovary." The cervix and cervical wall showed collections of similar neoplastic cells in the muscular portion of the structure. The mucosa was also the seat of chronic inflammatory infiltrate, and there was evidence of cervical erosion.

The tubal mucosa and muscularis were congested and edematous. The peritubal fibrous adhesions, described above, contained small nests of neoplastic cells similar to those described in the myometrium.

The solid portions of each of the ovaries were composed of oval and large round cells, each of which was clearly outlined without intercellular matrix. These cells had replaced the normal structure of ovarian tissue. They grew in small and large groups, and also displayed a tendency to eccentric displacement of their nuclei, giving the cells a signet-ring appearance. They produced considerable colloid which in some portions of the neoplasm became its outstanding feature. Although young fibrous tissue was found growing between small strands of these neoplastic cells, the latter stood out clearly as separate elements and showed no evidence of origin from mesodermic structure. In many of the sections were found hemorrhagic extravasations which had produced pseudocysts. Acinar structure or glandular architecture could not be demonstrated in any of the sections.

The vessels of the broad ligament were congested, and there were areas of recent, as well as old, hemorrhagic extravasations. Foci of neoplastic cells, similar to those previously mentioned in the tube and uterus, were found irregularly distributed throughout the section.

There was an increase in the fibrous tissue of all layers of the appendix. Collections of neoplastic cells identical with those described in the ovary were found singly or in groups filling the lumina of lymph capillaries of the serosa, muscularis, and submucosa. The metastasis was obviously from the serosa toward the inner layers of the organ, along the perivascular lymphatics.

*Diagnosis.*—(1) Krukenberg tumor of ovaries, uterus, and adnexa with metastasis to appendix; and (2) erosion of cervix.

*Laboratory Data.*—Urinalysis was normal. Blood counts showed red blood cells to be over 4,000,000 per c.mm. The hemoglobin was 62 per cent. The color index was 0.7 per cent. The leucocytes varied between 8,800 and 13,600 per c.mm. with a normal differential count. The sedimentation time was 7 mm. in one hour. The blood chemistry showed sugar 125.0 mg.; urea nitrogen 24.0 mg.; uric acid 4.5 mg.; and the creatinine 1.2 mg. per 100 c.c. The Kahn and Klinc tests were both negative. The blood was determined to be Group A.

The patient's condition was good throughout the operation. She reacted well, was out of bed on the thirteenth day, and was discharged on the fifteenth day following operation.

Following her discharge from the hospital she received two exposures of deep x-ray therapy, but could not continue with radiation because of the abdominal pain, nausea, and general weakness.

On October 27, she was admitted to another institution with symptoms of intestinal obstruction which x-ray revealed to be in the rectosigmoidal region. On



After this operation the patient showed general improvement, gained in strength, and was finally up and about. However, following an attack of circulatory collapse, she died on Nov. 23, 1937.

### DISCUSSION

Since no post-mortem examination was performed on this patient, one cannot state definitely the primary origin of this neoplasm.

A point of interest in this case is the extensive lymph metastasis to associated and adjacent pelvic structures. Not only were the cervix, tubes, and uterus involved, but also the appendix, which is rarely mentioned as one of the sites of metastasis in this condition. Stone,<sup>2</sup> in a study of 133 cases of Krukenberg tumor, refers to only one with appendiceal involvement, reported by Amann. Another instance of appendiceal involvement was described by Andrew who thought that he had made the discovery of a primary Krukenberg tumor of the appendix when he noted the characteristic epithelial cells in its wall. Upon further investigation, however, the primary seat of the malignancy was found to be in the stomach. The microscopic examination of the appendix in our case showed a similar type and degree of involvement. It is quite probable, therefore, that in the past, similar appendiceal lesions were overlooked by others merely because the appendix did not show any gross changes. This may also account for the apparent infrequency of involvement of some of the other pelvic and abdominal structures which heretofore were believed to be rarely involved in cases of Krukenberg tumors, an observation still considered by some of the writers to be intriguing and difficult to explain.

### SUMMARY

1. The observation is made that metastatic involvement of the appendix, a supposedly rare complication which was found in this case, is probably a more common occurrence than is generally believed. This is probably also true of other structures hitherto considered to be rarely the seat of metastasis in this malady.

2. Detailed reports of many more cases of Krukenberg tumor than are at present available are necessary in order to solve some of the important problems arising in connection with this neoplasm.

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**Simons, R. D. G. P.**: The Serologic Investigation of Syphilis During Pregnancy, Nederl. tijdschr. v. geneesk. 82: 5210, 1939.

Simons points out that the incidence of syphilis in the maternity hospitals of Holland is very small because women are not admitted until after the eighth month of pregnancy. Practically all these women are free from syphilis because most of the syphilitic women abort before the eighth month. The exceptions to this rule are women who have had a number of abortions and premature labors but finally deliver a full-term child who has syphilis.

Therefore, the routine serologic examination for syphilis does not belong in maternity hospitals, but should constitute a part of prenatal care just as the search for albuminuria which occurs only twice as frequently as syphilis. It should not be the congenitally syphilitic child which brings the maternal syphilis to light, but the doctor should do this.

J. P. GREENHILL.

October 30, a right transverse colostomy was done as a palliative procedure by another surgeon. At that time, carcinomatous nodules were found in the omentum, and a moderate amount of fluid was present in the peritoneal cavity. A biopsy taken at this time was reported as "omental implant of carcinoma."

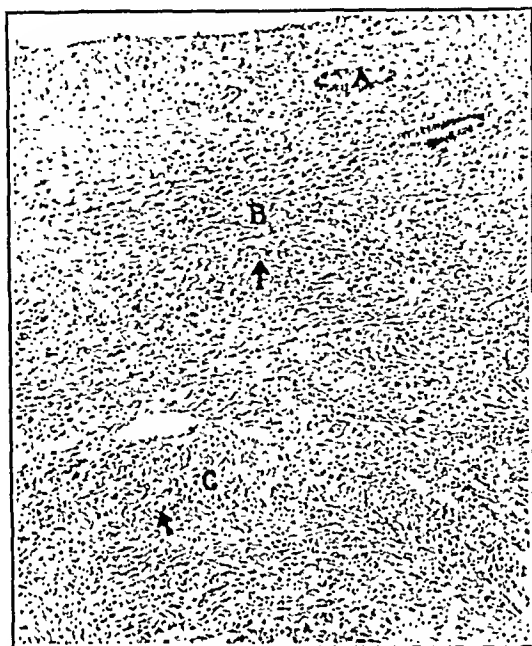


Fig. 4.—A representative section of the uterus showing endometrial glands (A). Arrows point to the nests of malignant signet-ring cells in the subepithelial layer (B) and in the myometrium (C) ( $\times 120$ ).



Fig. 5.—A portion of a cross section of the appendix showing the mucosa (A), the submucosa (B), and circular layer of muscularis (C). Arrow points to clusters of malignant epithelial cells similar to those described above, infiltrating the submucosa along perivascular lymphatic channels ( $\times 80$ ).

Varying in symptoms and signs from other ovarian tumors because of its endocrine basis, the granulosa cell tumor causes a premature growth of pubic and axillary hair, menstruation, breast changes, enlargement of the genitalia, and a change from the girlish to the adult female formation. Where the only symptom is that of tumor, a differential diagnosis may be difficult, as it is necessary to differentiate these tumors from those of the omentum, mesentery, kidney, spleen, liver, and also abdominal ascites. All of the above diagnoses were considered in the following case and the one given preference was that of a large omental cyst.

The patient was 9 years of age, colored and gave a history of a bilateral parotitis of a week's duration. Four days before admission to the Children's Hospital, the mother, while bathing her, noticed a large abdominal tumor. A laxative and an enema were given without result, and, noticing the presence of fever, she brought the child to the hospital. The previous history was that of a normal healthy child without a serious illness and without symptoms referable to the abdominal tumor other than recent slight abdominal discomfort. Physical examination revealed a normally developed child who was slightly underweight and did not appear acutely ill. The breasts were undeveloped and other evidence of precocious sexual development was absent. Palpation of the abdomen revealed a large tumor which filled the pelvis and extended upward to a point well above the umbilicus. It was slightly movable and found to be irregular on the lateral aspects. The tumor was very firm in consistency and had the shape of an enlarged uterus. Roentgenograms of the kidneys, ureters, and bladder revealed a dilatation and obstruction of the right ureter and right kidney pelvis with a distortion of the bladder. Roentgenographic evidence of a large abdominal mass was found on an x-ray plate which gave an appearance similar to that of a mesenteric cyst. The red cell count was 4,430,000 and the hemoglobin was 74. The leucocyte count was 14,650 of which 72 per cent were polymorphonuclears, 3 band forms being present. A syphilitic history was denied and a Wassermann test was negative. An Aschheim-Zondek test was negative. The nonprotein nitrogen present in the blood was 24 mg. per 100 c.c. and results of an examination of the urine were normal. The temperature was 100.4° F., pulse 110 and respiratory rate 25. After careful preparation which consisted of rest in bed, transfusions and a high caloric diet designed to leave a small residue in the intestinal tract, operation was performed.

A midline incision was made, extending from the pubis to a point just below the umbilicus curving left and extending well above the umbilicus. The tumor found was nodular, solid and arose from the left ovary and included in its mass the upper one-fourth of the bladder. It filled the pelvis and extended several centimeters above the umbilicus. A complete removal was carried out, which necessitated a resection of about one-fourth of the bladder. Following operation, an obstruction of the small intestine developed and rendered a second operation necessary. This was carried out on the eleventh postoperative day. Thirty-nine days after the first operation the patient was discharged from the hospital. Roentgen therapy was started before the patient left the hospital and was continued following discharge, yet in less than eight weeks from the time she left the hospital a metastasis was found in the line of incision and death occurred in five months from the time of operation.

The pathologists, Drs. Lindsay, Riee, and Sellinger, reporting on the tumor removed at operation, made a diagnosis of mucoid carcinoma. It weighed 1,650 Gm.

*Pathologic Report.*—*Gross:* The specimen was a rounded irregular mass of neoplastic tissue, varying between 13 and 20 cm. in circumference and weighing 1,650 Gm. The tumor was made up of many grayish white and bluish gray pedunculated firm masses of fibrouslike tissue. The color of the dark areas was believed to be due to hemorrhage. Tags of fibrous tissue were adherent to the surface.

On section the greater portion of the mass was made up of whorls of firm grayish white homogeneous tissue. The interior and one portion of the periphery were of a loose texture with dirty gray discoloration presumably due to hemorrhage or increased vascularity. At one portion of the tumor, 3 cm. from the surface, was an open space filled with a blood clot.

In one portion was found a pocket apparently lined with epithelium and believed to be a portion of the bladder wall.

*Microscopic:* Paraffin sections consisted of irregularly branching strands of connective tissue stroma, varying in density. These strands enclosed and supported

## CARCINOMA OF THE OVARY IN A CHILD NINE YEARS OF AGE\*

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AN OVARIOTOMY was performed on a child by de Giralde in the year 1866, reported in 1869, and is, according to Brun, the first recorded case. Kelly stated that Wells removed an ovarian cyst from an eight-year-old girl in 1882 and that Sims in 1883 removed such a tumor which weighed 61 pounds. The age of Sims' patient was eleven and one-half years and her weight after removal of the cyst was 76 pounds. Kelly states that Koeberle reported a case in 1876 and that Henning in 1878 was able to collect four cases of this operation having been performed in children. Saint Anna, it is stated by Bourde, performed an ovariectomy for a tumor in a child eighteen months of age in 1884. Two patients of Johnson's prior to 1890 who were operated upon are reported by Kelly. Wiel in 1904 reported 60 cases of ovarian tumors occurring in children of ten years of age and younger, of whom 24 were under five years of age. Downes in 1921 collected 26 additional cases of ovarian tumors occurring in children of ten years of age or less. Loeb and Levy reported 35 cases from the literature between 1921 and 1931. Witzberger and Agerty in a comprehensive review of the literature in 1937 reported 186 cases.

Ovarian tumors though rare in childhood are not medical curiosities. The Children's Hospital in Washington, D. C., during the past ten years has admitted 42,864 cases, of which the case of ovarian carcinoma I am reporting was the only ovarian tumor in the group. Cases have been reported by Cahill and Shearer, however, from other Washington hospitals and the two cases of Johnson reported by Kelly occurred in this city. Lanman writes that in 12,260 admissions to the Boston Children's Hospital in the surgical division, there were 5 cases of ovarian tumors. One of the least frequent of all tumors occurring in the admissions at the Washington Children's Hospital it is also true, quoting Gardner's series of 607 ovarian tumors, that in so large a series few tumors of this nature are found in children. The youngest patient Gardner reported was six years of age, the total number found between the ages of six and twenty was 34. Walfrido de Leon reported but two cases of carcinoma in children in 1,502 malignant tumors, of which 1,267 were carcinomas. There were, however, 12 sarcomas and 7 miscellaneous tumors in this age group. None of these tumors were of the ovary. Witzberger and Agerty found 22 cases of sarcoma and 25 cases of carcinoma in their series of 186 reported cases, 7 of the latter being granulosa cell tumors. According to these authors there was no absolute increase in frequency as the age increased. Seven tumors were reported in infants under one year of age. Dodek reported a case in 1933 of an ovarian cyst, reaching such a large size in the fetus as to cause its rupture at birth, occasioning death of the child and drawing attention to the intrauterine development of these tumors infrequently seen. Dermoid cysts constituted 24 per cent, teratomas 7 per cent, hemangiomas 0.5 per cent, and chorionepitheliomas 1.5 per cent of Witzberger's and Agerty's series.

The symptoms of children suffering from these tumors are frequently late in developing, the presence of a tumor being a frequent first discovery. Pressure on the rectum or bladder, according to McNamara, Henneger, and Lytle, is seldom present, because in children the ovary is an abdominal rather than a pelvic organ. Abdominal pain of varying severity may be present as may a slight loss of weight. Anemia, constipation, and diarrhea are late symptoms and are usually due to metastases. Witzberger and Agerty call attention to the fact that the pain from a twisted pedicle may be very severe and be confused with an attack of appendicitis.

\*Read, by invitation, at a meeting of the Washington Gynecological Society, December 3, 1938.

which the abundant cytoplasm was stained pink, and with the large somewhat irregularly staining nuclei, suggested the appearance of ganglion cells. Similar cells were scattered through the denser areas described above, and among these, also, were seen vacuolated, presumably mucoid cells. A "perivascular" arrangement also appeared at a number of points. While it was possible that this tumor represented several types of cells, as in a teratoma, it was considered more likely that it was a mucoid carcinoma and that the variation in cell types was due to various stages of cell activity. The process was histologically definitely malignant. The extensive mucoid changes suggested a high degree of differentiation, and these with the apparent gross complete encapsulation were favorable factors. However, it being understood that the tumor could not be removed entirely, the known frequency of involvement of both ovaries in such cases and the recognized general tendency to recurrence and metastasis were distinctly unfavorable. The condition was also most likely highly radioresistant though roentgen treatment might be considered.

*Diagnosis:* Carcinoma, mucoid.

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### ECTOPIC DECIDUA IN THE VERMIFORM APPENDIX\*

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THE finding of ectopic decidua in the appendix has been reported infrequently. Such a finding was first noted by Hirschberg<sup>1</sup> who described ectopic decidua of the vermiform appendix in association with right tubal pregnancy. Here the appendix was adherent to the tubal mass and the decidua probably reached the serosal surface of the appendix by direct extension. Weller<sup>2</sup> states that both endometriosis and decidual reactions are more frequently encountered in the appendix than the literature would indicate but gives no incidence of figures nor cites any case reports.

Endometriosis of the appendix is a well-established entity and has been frequently reported in recent years.<sup>3-6</sup> It is readily understandable that such misplaced endometrial tissue should undergo decidual change under the hormonal stimulation of pregnancy. The development of decidua without any evidence of preexisting or co-existing endometrial tissue is somewhat more difficult to explain. Decidual reactions have been found in the cervix,<sup>7</sup> especially around the external os,<sup>8</sup> and several times within cervical polyps.<sup>9</sup> Weller explains the formation of decidua from pre-existing endometriosis on the fact that the cytogenic stroma of misplaced

\*Presented at a meeting of the Chicago Gynecological Society, November 17, 1939.

islands of cells which were for the most part irregular in their morphology, and had irregular, hyperchromatic nuclei, frequently with large nucleoli. Mitotic figures were not common. There were also many areas in which the cells were large, vacuolated, the nuclei crowded to one side, giving the typical picture of "signet ring" cells characteristic of mucoid degeneration. In still other areas there were many cells, in

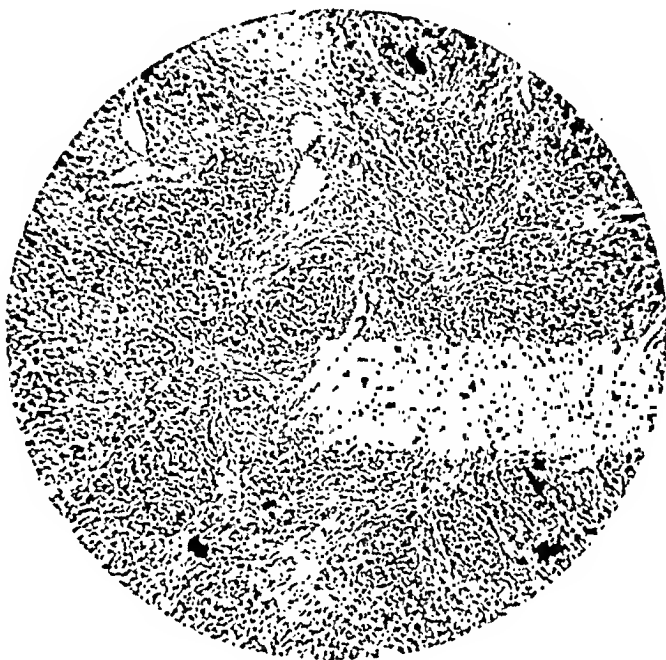


Fig. 1.—Section of ovarian tumor; low power.

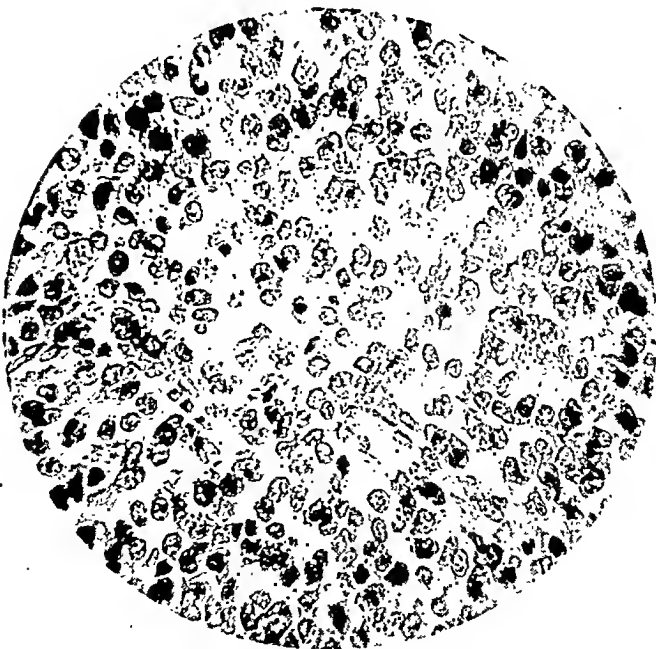


Fig. 2.—Cellular area, high power.

McBurney's point and displacement of the uterus to the right reproduced pain in the right lower quadrant. Temperature at that time was 98.4° F. by mouth and the leucocyte count, 12,100. The patient was put at rest and the pain gradually disappeared during the next several days. The pain recurred the following week, June 20, but the localized tenderness was less marked than previously; leucocyte count was now 14,150. Roentgenologic studies at this time revealed tenderness on palpation over the ileocecal valve, but it was impossible to visualize the appendix, six hours after the barium meal. Twenty-four hours later fluoroscopic examination again showed marked tenderness over the cecum, corresponding to the anatomic location of the base of the appendix. During the following four weeks, the patient had three more similar attacks of right lower quadrant pain with definite tenderness medial and superior to McBurney's point. Each of these succeeding attacks of pain subsided under restricted activity. On Aug. 15, 1939, during the patient's thirtieth week of pregnancy, an attack of pain began which was much more severe than at any time previously. Tenderness was more marked than in previous attacks; temperature was 99.8° F. by mouth, leucocyte count, 11,500. Because of the persistence of pain and tenderness for seventy-two hours and the slight elevation of temperature, an appendectomy under cyclopropane anesthesia was performed through a muscle splitting incision at the umbilical level. The appendix was found lying transversely and was acutely angulated in its middle third; the distal third appeared bulbous, markedly reddened, and seemed rather velvety in appearance. The patient made an uneventful recovery and was discharged from the hospital on the twelfth day. She was readmitted in active labor on Oct. 28, 1939. Delivery of a full-term baby girl was spontaneous with an episiotomy. The puerperium was uneventful.

Examination of the appendix showed it to be 4 cm. in length, the external surface of the proximal two-thirds being gray pink, smooth, and glistening. The wall was moderately firm and the lumen contained some feces. The distal third of the appendix showed several focal granular and hemorrhagic areas.

*Pathologic Report.*—(Dr. Otto Saphir.) "Microscopic: The mucosa, submucosa, and muscularis show no histopathologic changes. Adherent to the serosal surface there are several localized, small, cellular nodules. These are composed of rather closely packed, large, round, oval or polygonal cells with distinct cell boundaries. They have pale, faintly eosinophilic cytoplasm which sometimes has a glassy appearance and centrally situated, oval, pale, vesicular nuclei. The latter usually contain one rather prominent nucleolus and a distinct chromatin network. These cells are epithelioid in type. They are embedded in a rather scant connective tissue stroma which contains many thin-walled blood vessels. The latter are markedly engorged with red blood cells. The serosa adjacent to these nodules is diffusely infiltrated with polymorphonuclear leucocytes and occasional lymphocytes. *Diagnosis:* Decidua of the appendix."

This is a report of a typical deciduallike tissue in the subserosa of an appendix removed during the thirtieth week of pregnancy. The decidua is typical in morphology. No evidence of endometrial tissue was found although approximately thirty sections were cut and examined.

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endometrial tissue reacts exactly like the inter-glandular stroma of the endometrium. He also feels that decidual cells may develop under hormonal stimulation from connective tissue, or from cellular elements of the subserosa. He believes that the subserous stroma cells possess "pluripotentiality in differentiation" and that therefore such cells may develop into either endometrial or decidual cells.

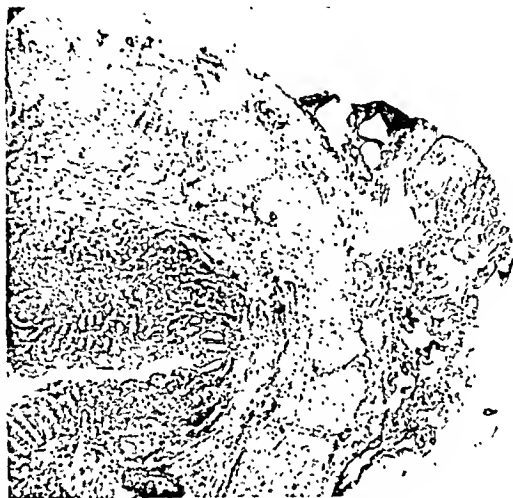


Fig. 1.—Ectopic decidua in subserosa of vermiform appendix.  $\times 13.6$ .

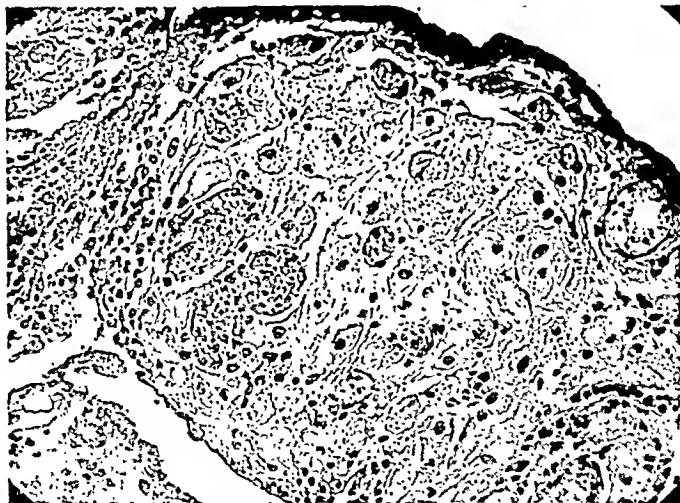


Fig. 2.—Same as Fig. 1. Note typical decidual cells, large cells, closely packed with pale, glassy cytoplasm. The pale, oval, vesicular nuclei show prominent nucleoli and distinct chromatin network.  $\times 210$ .

It is obvious that the finding of decidual tissue in the subserosa of the appendix must be an uncommon finding because the combination of appendicitis and pregnancy is uncommon. The occurrence of decidual tissue in an appendix removed during pregnancy prompts this report.

#### CASE REPORT

Mrs. H. K., a 23-year-old primigravida, whose last menstrual period began Jan. 21, 1939, was admitted to the Michael Reese Hospital on Aug. 17, 1939, complaining of pain in the right lower quadrant of the abdomen. The first attack of similar pain was on June 6, 1939, at which time the patient was in her sixteenth week of pregnancy. At that time there was slight nausea, marked tenderness over



complicated by pyelitis, abscess of the left axillary space, and a morbidity of fifteen days. Upon discharge, the abdominal incision had healed by first intention. There appeared blanched areas near the incision, similar to those over the inguinal regions as a result of the radium treatment. The lesion of the vulva had decreased in size to about 1.5 cm. in length, and 1 cm. in diameter. A large amount of yellow leucorrhea was present. All complications resolved.

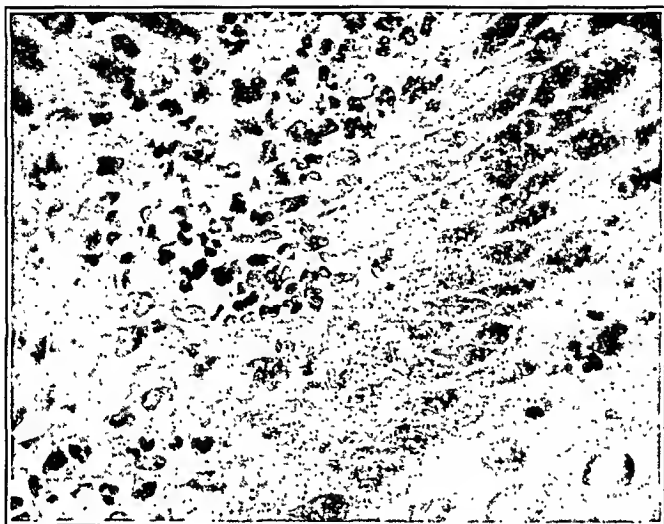


Fig. 1.—Microphotograph of the biopsy which shows the mitosis and variation in the size of the cells. ( $\times 725$ .)

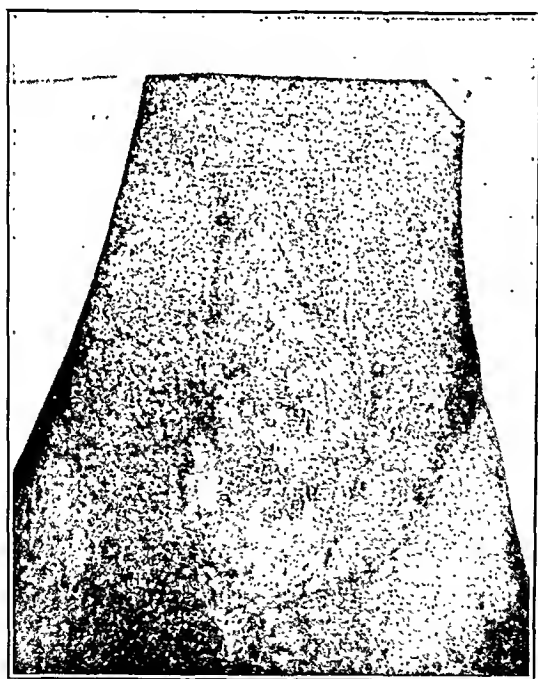


Fig. 2.—This mass in the gross was 4 cm. in length, 3 cm. in width, and protruded about 1.5 cm. above the skin surface.

The patient received seven treatments with roentgen rays, totaling 1764 r. units between May 9 and Oct. 24, 1934.

She was admitted to the Hospital on Oct. 23, 1934, at which time her temperature was 97.2° F., pulse 82, respirations, 20, and blood pressure 98/66. A physical

# CARCINOMA OF THE VULVA COMPLICATING PREGNANCY

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CARCINOMA of the external genitalia in the young is very rare indeed and even more so when it is primary. Still rarer are the primary carcinomas of the external genitalia complicating pregnancy. There are but two cases of the latter type reported in the literature to date, but more must have occurred. Tuft<sup>1</sup> reported the first carcinoma of the vagina complicating pregnancy in 1930. Two others were vaginal in type, but the vulva was involved in this case which is the first of this type to be reported. The age of the patients is another unusual feature. Baldwin<sup>2</sup> reports the youngest patient. It is a rather unusual and interesting fact that all three patients were under the age of eighteen years.

I submit the following case as a true carcinoma of the vulva complicating pregnancy:

J. M., a 17-year-old primigravida negress, was admitted to the John Gaston Hospital from the Clinic for observation and treatment of a growth on the left labium majus about the size of a lemon. Her last regular menstrual period occurred on Sept. 28, 1933. The patient was in the seventh lunar month of pregnancy, which was uncomplicated except for this newgrowth. She first noticed a "knot" on the left labia in December of that year which was associated with a bloody vaginal discharge. This persisted until she was admitted to the Hospital on March 5, 1934. There was no pathology of the freely movable cervix and the lesion was confined to the lower third of the posterior vaginal wall and left labia (Fig. 1). There were no other lesions found in the genital tract.

Her past history was essentially negative. At the time of admission the temperature was 98.6° F., pulse rate 80, respiratory rate 20, and blood pressure 110/70. The fetal heart rate was 144 and in the lower left quadrant. Blood examination showed 65 per cent hemoglobin, red cells 3,140,000, white cells 7,840, and no abnormal cells were found. Kahn test was negative. The catheterized specimen of urine was essentially negative.

A biopsy was taken and the pathologic report was as follows: "A rather dense connective tissue stroma, partially covered along one edge by stratified squamous epithelium. The latter structure shows considerable elongation of its rete pegs with fingerlike processes extending far down into the stroma. The cells composing these processes show mitotic figures and considerable variation in size, shape, and staining properties. These cells can only be made out with difficulty due to the tremendous accumulation of polymorphonuclears and small round cells in the stroma. *Diagnosis, squamous cell carcinoma.*"

After the biopsy report, radium bombs were inserted into the vulval lesion and inguinal regions, as follows: Vulva (in lesion), 1638 mg. hours; left inguinal region, 773½ mg. hours; and right inguinal region, 728 mg. hours.

The patient had an uneventful postoperative course and was discharged from the Hospital on April 2, 1934. The lesion was approximately 2 cm. in length, 1.5 cm. in width, and appeared to be elevated about 0.5 cm. above the skin surface at the time of her dismissal. It had lost its cauliflower appearance and was practically uniform in contour with no marked induration at its base. She was to return at weekly intervals for observation. Her weight was 125¼ pounds.

She was re-admitted to the Hospital on April 22, 1934 at the onset of labor. The membranes were intact with no vaginal bleeding. All laboratory and physical findings were practically the same as above, the blood pressure having increased to 150/110. She was taken to the delivery room where a normal, full-term, living female was delivered by a high classical cesarean section, the indication for which was the squamous cell carcinoma of the vulva. The adnexa were normal. Tubal ligation was performed by a modified Blundell technique. The puerperium was

their target. With this assurance the investigator formerly assumed that the cause of the sterility was found above the cervix, and most likely due to closure of the Fallopian tubes.

However, this cervical test, as good as it is, is really incomplete. The uterine cavity above the internal os of the cervix, should also be investigated for the presence of spermatozoa to ascertain whether they have penetrated through the thick, tenacious, mucus plugs which sometimes hinder the passage of the entering spermatozoa. In many instances spermatozoa have reached the cervical os, and have been prevented from traveling farther than that point. A marked leucorrheal discharge, together with stenosis or atresia of the internal os could constitute a hindrance to weakening penetrating spermatozoa. Aspiration of the uterine cavity and the finding of living spermatozoa would be far more enlightening than the mere finding of the spermatozoa in the cervical os. However, investigators have experienced much difficulty in obtaining specimens from the uterus without introducing into the uterus possibly infectious material from the cervix. No instrument has been devised which could penetrate the cavity of the uterus without first entering the cervical os and probably carrying some of its contents into the uterine cavity. Aspiration of the uterine cavity with a technique assuring the investigator that no living spermatozoa could have been carried through from the vagina or cervix is therefore the method of choice.

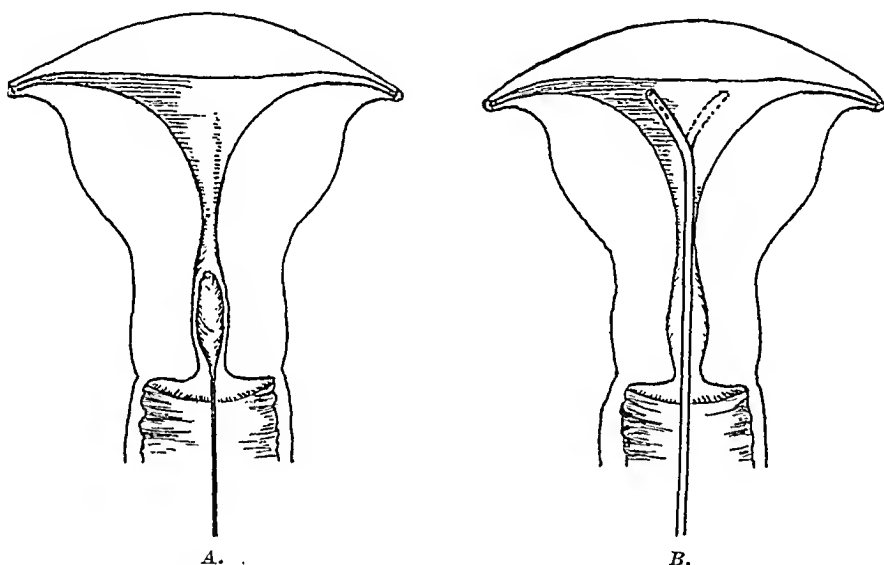


Fig. 1.—A, The applicator soaked with dilute lactic acid solution in place in the cervical canal. B, The uterine cannula used in aspiration of the uterus for spermatozoa.

*Technique.*—The patient is seen at the physician's office on the day previous to the test. She is instructed at that time in the use of the diaphragm pessary. She is also instructed to insert the clean rubber pessary immediately following coitus to retain as much of the seminal fluid as is possible. This is done not only to be certain that as much of the spermatozoa be kept in contact with the external os as is possible, but also to retain most of the semen within the vaginal canal, to neutralize the vaginal acidity and permit easier travel for the spermatozoa. She is also instructed to remain on her back and keep her legs flexed on her thighs for some time following intercourse, in order that the cervix is bathed in the seminal pool. The patient then presents herself about three hours after coitus (not sooner), since at that time all the spermatozoa in the vaginal canal should be dead. The diaphragm is then removed and the vagina is swabbed out with cotton balls, and the external surface of the cervix is wiped clean with a fresh cotton pledget. The vagina is carefully scrubbed with tincture of green soap, and irrigated. The vaginal part of the cervix is painted with iodine. The unsterile bivalve speculum is now removed and a second sterile vaginal speculum is inserted

examination was negative except for a midline incision and an indurated, fungating mass of the vulva. The blood examination revealed red cells 4,210,000, white cells, 8,650, and hemoglobin 14.2 gm.

A vulvectomy with the excision of the inguinal glands was accomplished with the canterry knife on October 26. The patient's convalescence was uneventful. A macroscopic examination revealed: "A specimen consisting of an irregular piece of pigmented skin and subcutaneous tissues comprising the labia majora and minora, clitoris, and the mass. A microscopic examination of four sections taken from various areas showed only slight edema and small round cell infiltration of the subcutaneous stroma. The thin layer of stratified squamous epithelium covering the tissues showed no evidence of malignancy. *Diagnosis:* Chronic inflammation, mild; non-specific."

The patient has been examined repeatedly during the past five years and there are no physical signs to suggest a carcinoma in any form. Her weight is normal. There was a mobile gland in the right inguinal region which has remained approximately 0.5 cm. in diameter for the past two years, but the patient refuses any further treatment. She has not conceived since the operation. A thorough physical examination of her child revealed no lesions and she was enjoying perfect health.

#### COMMENT

1. This case is reported with the belief that the patient has been cured for a period of five years.

2. A high classical cesarean section was performed in order to avoid dissemination of carcinomatous cells.

3. It is believed that sterilization of this patient was indicated because further pregnancies would favor metastasis if any malignant tissues remained and therefore shorten the life of the individual.

We are greatly indebted to Dr. Frank Smythe of the University of Tennessee who performed the excellent gynecologic work on this patient.

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## A TECHNIQUE FOR ASPIRATING VIABLE SPERMATOZOA FROM THE CAVITY OF THE UTERUS AS A FURTHER STUDY IN SPERM BEHAVIOR

### A PRELIMINARY REPORT

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HUHNER, in 1913,<sup>1</sup> reported a postcoital technique to obtain living spermatozoa from the cervix of the uterus in cases of suspected sterility. The technique, of which there are many variations today, consisted of the insertion of a bivalve vaginal speculum, location of the cervix, and obtaining of a specimen from the cervical os by means of an ordinary platinum loop on a glass rod. The specimen was placed on a glass slide and examined immediately under the microscope. The finding of normal viable spermatozoa eliminated the male from the responsibility for the sterility. With this technique many of the supposed causes of the sterility could be immediately removed from the list of etiologic factors. Little did it matter if the spermatozoa were deficient in numbers, or whether there was a hypospadias, epispadias, hyperacidity of the vagina, etc., as long as the spermatozoa had reached

placenta previa was ruled out by vaginal examination. She was dismissed after three days of rest in bed and re-admitted as a dispensary patient. At this time, June 17, 1935, roentgenographic study of the abdomen was done because of the seeming multiplicity of fetal parts as well as excessive enlargement of the abdomen. An anteroposterior plate of the abdomen revealed a single pregnancy, vertex presentation.

The patient was admitted to the hospital June 23, 1935, at 2:30 A.M. in active labor, with cervix fully dilated and membranes ruptured. After being taken directly to the delivery room, she was delivered normally of a living male child, weighing 6 pounds, 7 ounces. Palpation of the fundus after this delivery revealed another fetus in the uterus. Artificial rupture of the second bag of waters revealed the presentation to be a single footling, which was converted into a double footling, and breech delivery of a normal living female child, weighing 6 pounds, 9 ounces, was completed. The placenta was of the dizygotic type. The patient was dismissed on the ninth postpartum day.

CASE 2.—Mrs. A. D., gravida i, para 0, aged 25 years, white, was first seen March 7, 1938. During the first four weeks of pregnancy, she had suffered with severe vomiting and had lost 20 pounds of weight, which she regained as soon as vomiting was controlled. With this exception her prenatal period was uneventful.

In the thirty-fourth week of gestation the height of the fundus measured 36 cm. Because of excessive enlargement of the abdomen and multiplicity of fetal parts, a roentgenographic study of the abdomen was suggested. An anteroposterior film of the abdomen revealed a single pregnancy in the vertex presentation. Because of the continuing enlargement of the uterus in size to 41 cm., coupled with the fact that a multiplicity of fetal small parts could be palpated, the x-ray report of a single pregnancy was disregarded and the patient advised that in all probability a multiple pregnancy was present.

She entered the Immanuel Hospital June 25, 1938, in labor, cervix completely effaced, two fingers' dilatation, and after eight and one-half hours of labor, she delivered a normal living male child, weighing 6 pounds, 6 ounces. Palpation of the fundus revealed a second fetus in the uterus. Artificial rupture of the second amniotic sac was accomplished and a fetal head palpated above the ischial spines, revealing the position to be R.O.T. Rotation to an L.O.A. was accomplished manually, and Kristellar expression was applied to fundus; this effected the delivery of a normal living male child, weighing 6 pounds, 9 ounces. Delivery of the placenta by Credè expression after repairing the episiotomy wound showed a placenta of the uniovar type. The patient was dismissed on the tenth post-partum day.

#### DISCUSSION

Perusal of the literature reveals very few cases of error in diagnosis of multiple pregnancy by means of the x-ray.

There are a number of factors which might hinder making a correct diagnosis of the condition by this means. However, G. W. Grier<sup>1</sup> states that very often in twin pregnancy, with a vertex-breech presentation, the ordinary 14 by 17 film is not large enough and very often the fetal pole situated in the uterine fundus is entirely lost on the film. This is very likely the condition in Case 1, in which the vertex presented at the inlet but the breech in the fundus was missed entirely.

Very often hydramnios accompanies a multiple pregnancy. In such cases the excessive amount of fluid produces a "haze" on the film that causes difficulty in interpretation of fetal structures, especially in an anteroposterior view.

Grier<sup>1</sup> agrees with Reinberger and Russel<sup>2</sup> that the anteroposterior view is often inadequate in diagnosing multiple pregnancy. In taking an anteroposterior view, the rays must pass through the abdominal wall and thick muscles of the back as well as bony vertebral structures.

In the lateral view, however, because the uterus occupies the anterior portion of the abdomen, the amount of total tissue which is penetrated is a great deal less than in the anteroposterior view. Better detail should also be obtained in the lateral view, because the rays must traverse the maternal abdomen twice.

and the cervix located. With these precautions it is extremely doubtful if any living spermatozoa could be introduced by any cannula from the vagina into the cervix or the uterus.

Two specimens are now aspirated from the uterus, the first one from the cervix uteri and the second from the uterine cavity. The cervix is grasped with a volsella forceps, and an ordinary sterile Rubin cannula is inserted into the cervix as for an insufflation test. The cervical contents are then aspirated by suction, using a 10 c.c. syringe. The contents of the aspiration are expelled on a glass slide and studied at once under the microscope for the presence of living, motile spermatozoa. Then the second specimen is aspirated. Prior to the introduction of a re-sterilized cannula into the uterine cavity a special preparation of the cervical canal is undertaken. First, a cotton applicator (Fig. 1, A) soaked in dilute lactic acid solution of a pH similar to that found within the vagina is introduced into the cervical canal (pH 3.5-4.5). The applicator is thoroughly whirled about the cervical canal and allowed to remain in the cervix for about five minutes. It is then removed and a dry sterile applicator thoroughly wipes out the cervix. This procedure is sufficient to kill all the spermatozoa that may be in the cervical canal. The Rubin cannula (Fig. 1, B) is then inserted into the cervix through the internal os into the cavity of the uterus. Aspiration of the uterine contents should reveal the uterus free from any living spermatozoa introduced accidentally from the cervix or vagina. The finding of living spermatozoa in the uterus after this procedure may assure the investigator that these spermatozoa penetrated the uterus by their own propulsion.

#### SUMMARY

A technique employing a lactic acid swabbing of the cervix uteri between the external and internal os is proposed for the aspiration of living spermatozoa from within the uterine cavity. With this technique, it is probable that if living spermatozoa are found in the uterus, they were not pushed into the uterus from the cervix by the examining cannula.

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817 WEST END AVENUE

## FAILURE OF ANTEROPOSTERIOR ROENTGENOGRAPHIC EXPOSURE IN MULTIPLE PREGNANCY

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ORDINARILY roentgenograms are accepted as confirmative of either the existence or non-existence of multiple pregnancy. In addition to establishing these facts, the x-ray is of further aid in determining the presentation of the fetuses when a diagnosis of pluriparity has been made.

Roentgenographic interpretation is a laboratory procedure, and as such cannot be infallible in revealing the facts sought after. Such has been our experience on two occasions. Therefore, we are reporting our findings in these two cases.

CASE 1.—Mrs. D. C., gravida iii, para ii, aged 32 years, was admitted to the Dispensary Service of the University Hospital for prenatal care. Physical and obstetric history and examination were all essentially negative. The ante-partum period had been quite normal, with the exception of vaginal bleeding on several occasions during the last trimester of pregnancy. On May 26, 1935, she was admitted to the hospital because of vaginal bleeding, the cause of which was not determined, although

hemorrhage. When seen shortly thereafter, the patient showed typical signs of acute blood loss, the cause of which was considered to be retained placental tissue.

She was transferred at once to the hospital and given an immediate transfusion of 600 c.c. of whole blood. While this procedure was in progress, a vaginal examination was done under aseptic precautions. The findings were as follows: "There was a slight but continuous trickle of blood from the uterus, which had a rather boggy 'feel,' and was the size of a two months' pregnancy. The cervix was patulous and admitted the finger. Just above the level of the internal os and extending posteriorly up into the uterus was a somewhat firm, adherent, spongy mass, which could not be dislodged by the finger. Two or three pieces of this tissue were forcibly removed with a sponge stick. As a consequence, rather free bleeding followed. Grossly the tissue was placental-like in character."

Since the mass seemed firmly attached to the uterine wall, it was felt that there was present either (1) an adherent placental polyp; or (2) a degenerating submucous fibroid, and that in either case hysterectomy was the procedure of choice. Consequently, as soon as preparations could be completed, a supracervical hysterectomy was done. Convalescence was satisfactory and the patient was discharged in good condition on the sixteenth postoperative day.

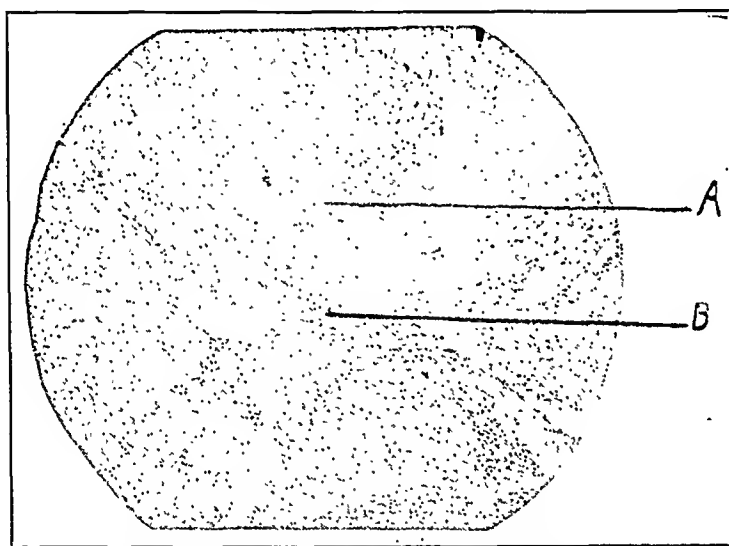


Fig. 1.—Low power section of uterus. A, Degenerated placental villi, B, myometrium.

*Pathologic Report.*—"The uterus measures 10 by 8 cm. The uterine cavity contains a polypoid mass measuring 3 by 1½ cm. At the upper end it is firmly adherent to the posterior wall midway between the fundus and internal os. On section the mass consists of grayish, rather firm tissue. The myometrium appears normal."

*Microscopic Examination.*—"One section shows placental tissue. Many of the villi are degenerated or necrotic. Another section shows the wall of the uterus. The muscle fibers in the myometrium are hypertrophied and the supporting tissue is infiltrated with polymorphonuclear cells. The endometrium has disappeared. A mass of degenerated placental villi and hyalinized fibrin is attached directly to the myometrium. There is some proliferation of the syncytial cells covering some of the villi."

*Pathologic Diagnosis.*—Adherent degenerated placental tissue.

#### COMMENT

Curtis designates placental polyp as "portions of placental tissue of varying size, which may be retained within the uterus for an indefinite period after abortion or full-term pregnancy." If retained for any length of time embedded upon the uterine wall, gradual necrosis of the tissue occurs. Proliferating chorionic epithelium

It may be reasoned that when the presentation of both children is cephalic, as in Case 2, one head must be posterior to the other, and therefore but one skull may show in the anteroposterior view. This would not be the case in a lateral view, since both vertices as well as their respective fetal skeletal structures would show very clearly, with no fetal part being superimposed one upon the other.

It, therefore, seems logical, if roentgenograms are to be relied upon in the diagnosis of multiple pregnancy, to insist upon a combination of the anteroposterior and lateral views as routine procedure, for the same reason that the surgeon demands these views before attempting the reduction of a fracture of one of the long bones.

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## LATE PUERPERAL HEMORRHAGE DUE TO PLACENTAL POLYP\*

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THE occurrence of placental polyp, causing hemorrhage severe enough to threaten the patient's life, is apparently infrequent. Reference to four standard textbooks on obstetrics showed one only, in which this condition was described. The literature on the subject is very meager, a few cases being reported chiefly by foreign observers. Owing to the paucity of records of a similar nature, I wish to report the following case.

#### CASE REPORT

Mrs. G. S., a 34-year-old white primipara, was delivered at term in the Methodist Hospital on Aug. 7, 1937. Her ante-partum course was uneventful. She had a hard labor of twelve hours' duration. Five and one-half hours before the baby was born, bright red vaginal bleeding occurred and continued in a steady trickle until two hours before delivery. Shortly after the bleeding began, vaginal examination revealed a small rim of cervix anteriorly, and the head above the spines in an L.O.T. position. The cause of the bleeding could not be determined, but it was thought to come from the cervix.

Directly after the birth of the baby there was a large gush of blood. Immediate inspection of the cervix showed, in the 5 o'clock position, a 1.5 inch tear, from the angle of which a bleeding vessel could be seen. Interrupted sutures closed the laceration and stopped the bleeding. The placenta presented no evidence of old clots or missing cotyledons.

On the third day post partum, the patient passed an orange-sized clot; on the seventh day the lochia seemed more than normal in amount. Otherwise nothing unusual occurred while she was in the hospital. She was out of bed on the tenth and went home on the twelfth day of the puerperium. Discharge examination at that time showed the episiotomy wound healed, lochia scant and rusty-colored, cervix somewhat patulous and uterus not completely involuted. She was advised to remain in bed for a few days at home.

Her stay there was uneventful until the morning of the seventeenth day post-partum, when she passed a blood clot "as large as one's fist." In the late afternoon a smaller clot was expelled. Nothing unusual occurred the following twenty-four hours, but the next afternoon on getting out of bed, she had a sudden, profuse

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\*Presented at a meeting of the Section on Obstetrics and Gynecology, New York Academy of Medicine, January 24, 1939.



The infant was in poor condition; weighed 2 pounds 11 $\frac{3}{4}$  ounces and was 38 cm. long. Examination revealed a long linear scar on the left side, extending from the malar bone upward along the face and scalp to a point close to the termination of the frontoparietal suture. At the upper part there was a small area of granulation tissue, but elsewhere the scar was well healed and contracted, tending to draw the nose and eye toward the side of the scar (Fig. 1). In addition, there was a talipes equinovarus of the right lower extremity. The infant was promptly transferred to the premature ward, where he died twelve hours after birth.

Post-mortem examination revealed no other anomalies. The cranial bones were intact.

The patient now, for the first time, admitted that twelve weeks prior to this hospital admission she had visited an abortionist who attempted to interrupt pregnancy with instruments. During this procedure the patient began to bleed moderately. The



Fig. 1.—Showing infant with facial scar. The left eye is pulled toward the contracted scar.

frightened abortionist immediately discontinued his efforts, told the patient that her pregnancy was too far advanced to permit interruption, and allowed her to go home. Her bleeding ceased after a few days, but approximately twelve weeks later on August 28 she fell down a flight of stairs and began bleeding again. The rest of the story has already been told.

The post-partum course of the mother was uneventful except for one rise of temperature to 101.4° F. on the fourth post-partum day. She was discharged home on the tenth post-partum day in good condition.

One may conclude from the above that a curette or similar instrument ruptured the patient's membranes and lacerated the face of the fetus when the patient was approximately twelve weeks pregnant. Then, with membranes ruptured, the fetus continued to live in utero another fourteen weeks before it was spontaneously expelled. A search of recent literature revealed no similar cases.

may be found surrounded by layers of organized blood clot and fibrin, the whole mass forming a polypoid tumor. Until the latter is removed, involution of the uterus is interfered with and hemorrhage results.

It is quite likely that bleeding late in the puerperium is more often due to such a polyp than is generally recognized. Possibly, too, the pathology may have its origin in accessory placental tissue such as placenta succenturiata or spuria. Rarely, however, would one expect to find such adhesive qualities as this polyp showed.

Manual removal or curettage is the usual form of treatment. In the present instance, the mass was too adherent for manual removal; curettage involved grave risk of injury to the uterus; active bleeding was in progress. Under the circumstances, hysterectomy was considered a lifesaving measure.

#### SUMMARY

The case here reported is unusual in that a dangerous hemorrhage late in the puerperium was due to an adherent placental polyp, and that hysterectomy was necessary to effect a cure.

52 EIGHTH AVENUE

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## PRENATAL INJURY OF THE FETUS

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**A**TTEMPTS to interfere with early pregnancy by means of direct instrumentation almost invariably result in the death of the ovum. This is followed either by complete or incomplete abortion, which may or may not be accompanied by a uterine infection. While instances in which pregnancy continues after instrumentation are seen with a reasonable frequency, this rarely happens if the amniotic sac is ruptured. The case here reported is unusual in that not only was the amniotic sac almost certainly ruptured at the end of the first trimester of pregnancy, but the fetus itself appears to have been injured. Nevertheless, the pregnancy continued until the twenty-sixth week.

The patient, J. D., a 29-year-old primipara, was admitted to the Obstetrical Ward of Bellevue Hospital on Sept. 19, 1937. The Wassermann reaction was negative. Her last menstrual period had been on April 8, 1937. She believed herself to be approximately twenty-four weeks pregnant. On August 28 she had fallen down a flight of stairs and immediately began to bleed. When admitted to the ward, approximately three weeks after her fall, she was not in labor but was still bleeding moderately without definite pain. A diagnosis was made of threatened abortion. The uterine fundus was now 2 fingers above the umbilicus. The fetus was lying in L.O.A. position with the head dipping slightly into the pelvis. The fetal heart was 150 and in the left lower quadrant. At this time the patient's erythrocyte count was 2.94 million, hemoglobin 70 per cent. She continued to bleed slightly, and a vaginal examination was done on September 23. The cervix was found to be  $2\frac{1}{2}$  cm. long and was soft. The lower segment felt normal and there was no evidence of a placenta previa. No membranes or bag of waters could be felt. On speculum examination a cervical erosion was present; on the posterior lip of the cervix there was a point from which dark blood oozed. This area was swabbed with acetone. She was returned to bed and given a blood transfusion. Because of almost complete cessation of bleeding no further therapy was instituted. On October 3 she spontaneously went into labor. After a first stage of eight and one-half hours and a second stage of fifteen minutes, she spontaneously delivered a premature male infant. Neither doctors, nurses, nor patient were ever aware of the membranes rupturing. It was certain that she had a dry labor.

## DISCUSSION

Torsion of the uterus is rare. As far as can be determined all the cases reported in the literature occurred in uteri which were either pregnant or myomatous. McIver and Buxton<sup>1</sup> state that torsion of the uterus is usually found in older women, that it is associated with leucocytosis, and that the torsion is generally clockwise. The degree of torsion varies, and Gordon-Watson and Shaw<sup>2</sup> report one case in which the fundus was twisted 450 degrees on the cervix. Hawes<sup>3</sup> and others emphasize that the condition is rarely diagnosed preoperatively, and the former suggests that the attempted passage of a uterine sound might be a diagnostic aid. Day<sup>4</sup> in discussing the condition associated with pregnancy states it is difficult to diagnose, the patient is usually in shock, there is rarely external bleeding, and there is frequently sudden pain in the right lower quadrant. Javett, Anderodias and Mahon,<sup>5</sup> Rabbiner,<sup>7</sup> and many others report isolated instances of uterine torsion complicating pregnancy and indicate it is frequently mistaken for premature separation of the placenta, a fact also brought out by Eastman.<sup>8</sup>

Fleischer and Kushner,<sup>9</sup> Battaglioli,<sup>10</sup> Erdmann,<sup>11</sup> and others have reviewed the literature and added instances of uterine torsion due to fibroids. In these types the diagnosis is likewise obscured before laparotomy is done.

The case reported is one of torsion of the nonpregnant, nonmyomatous uterus, caused, undoubtedly, by an adhesion. It has been detailed because it appears there is no similar torsion of the uterus reported in the literature.

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## SPONTANEOUS RUPTURE OF PAPILLIFEROUS CYST OF THE OVARY

### REPORT OF A CASE

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(From the Surgical Service of The Bronx Hospital)

**A** SUDDEN, spontaneous rupture of a papillary cyst of the ovary occurs rarely.<sup>1</sup> A. C., a 60-year-old, white, married, Jewish woman, was admitted to The Bronx Hospital at 11 P.M. on Sept. 29, 1939, complaining of abdominal pain and distention. The patient had been perfectly well until 1 P.M. of the same day when, following her luncheon, she had a sudden onset of a sticking pain across the upper and lower third of the abdomen, associated with distention. The pain was continuous and did not radiate. It was relieved somewhat by the application of a hot water bag. At 4 P.M. she took an enema and attempted to induce emesis with a dose of sodium bicarbonate and lemon juice. Both of these measures relieved the symptoms slightly. At 8:30 P.M. she repeated the enema and, following this, the abdominal pain completely disappeared and the distention diminished. There was at no time any nausea, vomiting, or elevated temperature, but there was anorexia. There was no history of trauma.

Ten years prior to admission, a cholecystectomy for cholelithiasis was performed at another hospital, with complete relief of symptoms. The menopause had occurred

## TORSION OF THE UTERUS\*

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NEW YORK, N. Y.

*(From the Department of Gynecology, Detention Hospital, Department of  
Correction)*

M. H., aged 32 years, colored, single, was admitted to the Gynecological Service of Detention Hospital on Nov. 25, 1936. The patient complained of pain in the abdomen for the past twelve hours. Past history included chronic gonorrhea treated for two or three years. Three years ago a high classical cesarean section had been performed, following a thirty-four-hour trial labor with a face presentation; the postoperative course had been stormy with temperature of 105° F. on the fourth post-partum day, and convalescence had been further complicated by left femoral phlebitis. She was discharged on the twenty-second day with a living female child.

Menstruation had been normal and the last menstrual period was two weeks prior to the present admission and lasted for three days. The patient began to bleed again on the day of admission to the hospital. There was no nausea, and the bowels moved normally the day of admission.

Physical examination disclosed a healthy looking young colored woman obviously in acute pain. Temperature was 102° F., pulse 96, respiration 24. Significant physical findings included irregular pupils; tachycardia; an old right rectus incisional scar; rigidity and tenderness in both lower quadrants of the abdomen, more on the right—a movable globular mass in the right lower quadrant; and moderate amount of uterine bleeding with a soft, boggy uterus, not well outlined.

Laboratory examinations disclosed blood Wassermann 4-plus; vaginal smear suspicious of gonorrhea; white blood cell count seven hours after the onset of pain was 5,700 with 71 per cent polymorphonuclears; three hours later it had dropped to 5,040 with 68 per cent polymorphonuclears; three hours later it had risen to 15,900 with 79 per cent polymorphonuclears; and urine disclosed 2-plus albumin with many white blood cells and frequent fine and coarse granular casts.

The preoperative diagnosis was acute appendicitis, pelvic inflammatory disease, or a twisted ovarian cyst.

As the patient was growing rapidly worse, and as an acute surgical abdomen presented, operation was performed on Nov. 26, 1936, sixteen hours after the onset of the pain.

*Operation.*—Under drop ether anesthesia a midline incision was made. The uterus was enlarged to the size of a six weeks' pregnancy; it was pulled upward and to the right and twisted upon the cervix 180 degrees in clockwise rotation. The left tube passed in front of the uterus and was inserted on its right aspect. A thick, dense, fibrous adhesion joined the right anterior surface of the fundus to the posterolateral parietal peritoneum on the right with omental involvement. The uterus was dark red, tense, and mottled with purplish petechiae. The adhesion was divided with sharp dissection, leaving a small amount of serosa and myometrium attached to the parietal peritoneum. The uterus was then untwisted and fixed in position by a Baldy-Webster suspension. The abdomen was closed in layers. Postoperative convalescence was febrile for the first six days, but the patient suffered no further abdominal discomfort.

\*Read at a meeting of the Section of Obstetrics and Gynecology of the New York Academy of Medicine, November 28, 1939.

operative day, she was allowed out of bed. At this time, the white blood cells were 11,500 with polymorphonuclear leucocytes 60 per cent, band forms 8 per cent, and lymphocytes 32 per cent. The red blood cells were 3,800,000 and the hemoglobin 72 per cent (Sahli). The urine showed a very faint trace of albumin. She was discharged on the fifteenth postoperative day. Twenty weeks after discharge finds her well and asymptomatic.

#### COMMENT

The case presented is unusual in many respects. The patient was 60 years of age, whereas most cystadenomas are found in women between 40 and 50 years of age. The clinical manifestations were those of a sudden, spontaneous, nontraumatic rupture of an ovarian cyst. In the absence of other causes, and, in view of the cyst contents found, the rupture was most likely due to a thinning of the cyst wall consequent upon degeneration and necrosis of that structure. In spite of the spill into the abdominal cavity of a large amount of highly irritating cyst contents, the abdomen was not drained, with uneventful wound healing and postoperative course. The tumor showed no invasion or malignant change despite the fact that the woman was in the cancer bearing age. There was no ascites, which occurs in 18.47 per cent of ovarian tumors with papillary surface growths. Cystadenomas are usually unilateral, but, where surface papillae exist, 60 per cent are bilateral and 50 per cent intraligamentous.<sup>2</sup> The tumor, therefore, had the criteria for bilaterality. However, since the other ovary was atrophic, its removal was not deemed necessary, though the current teaching is to remove the unaffected ovary prophylactically in all cases of cystadenomas, regardless of age, except where offspring are desired.

I am indebted to Dr. William Kline for permission to report this case.

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## BRONCHOSCOPY AS AN ADJUNCT IN THE TREATMENT OF ACUTE PULMONARY EDEMA COMPLICATING ECLAMPSIA

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EDEMA of the lungs is an emergency which the physician must be prepared to face in every case of eclampsia. It is said by Teel and others<sup>1</sup> to occur in 30 per cent of all eclamptic patients. Women with "eclampsia without convulsions" appear to be in even greater danger of developing the complication than those with the classical type of eclampsia, and it has been observed in pregnant and puerperal women who were wholly without demonstrable toxemia. The absence of valvular heart disease or of a history of hypertension or nephritis is no guarantee that acute pulmonary edema will not develop.

In a case recently under my care, the bronchoscope was introduced to enable fluid to be aspirated from the lungs. The patient recovered and it was felt that her life had been saved by the resort to this novel adjunct to treatment. So far as I know, the present is the first reported case in which therapeutic bronchoscopy has been used to combat pulmonary edema, although I am informed it was employed for this purpose previously elsewhere.

Mrs. J. J. P., white, aged 26 years, primipara at full term, was admitted to the Kentucky Baptist Hospital June 25, 1938. She had previously been under our care for rheumatic heart disease with mitral stenosis without hypertension. She gave a history of frequent fainting spells in the past two weeks, with cyanosis, slight cough for two or three days, and generalized edema without albumin in the urine. She was not yet in labor. Examination of the chest showed bronchial

twenty years ago. Since then, there was no vaginal bleeding or discharge. Urinary symptoms were absent. She was chronically constipated, but there was no obstipation. Effort dyspnea was present.

Physical examination revealed an obese, well-developed, well-nourished patient, who did not appear ill. The rectal temperature was 100.4° F.; the respirations 20 per minute, and pulse 80. There was no scleral jaundice. The mouth was edentulous, and the tongue dry. There was dullness over the bases of both lungs posteriorly, with a moderate number of medium moist râles, greater in the left than in the right. The breath sounds came through normally. The heart was not enlarged. A rough systolic murmur was present over the entire precordium, loudest over the pulmonic area, and transmitted to the vessels of the neck. Regular sinus rhythm was present. Blood pressure was 118/58. Abdominal examination revealed a healed right upper quadrant scar. The abdomen was moderately distended but soft. Rigidity and tenderness were absent. Rebound tenderness was present in both lower quadrants, the left being greater than the right. There were no masses palpable. Liver and spleen were not felt. There was slight left costovertebral tenderness. The extremities showed slight thickening of the peripheral vessels. The urine contained a faint trace of acetone, and an occasional red and white blood cell. The white blood count was 13,250 with 80 per cent polymorphonuclear leucocytes, 4 per cent band forms, 14 per cent lymphocytes, and 2 per cent monocytes.

The following morning, the temperature had risen to 101° F. At 11:30 A.M., both lower quadrants had become rigid and tender. A mass was palpable in the left lower quadrant. At this time, a flat plate of the abdomen showed moderate amounts of gas in the large and small bowel. The clinical impression was either a perforated bowel carcinoma or a twisted ovarian cyst. Immediate exploration of the abdomen was decided upon.

*Operation.*—At 1:30 P.M., laparotomy under spinal anesthesia was performed by Dr. Sidney Grossman. A five-inch hockey-stick shaped incision was made in the left lower quadrant. As the peritoneal cavity was entered, a large amount of turbid fluid gushed out. This was followed by a discharge of grayish, puttylike material, characteristic of the material seen in a dermoid cyst. The left adnexa were atrophic. A large cystic mass, the size of a grapefruit, was situated posterior and to the right of an atrophic uterus in the cul-de-sac of Douglas. Spontaneous perforation was present in the roof of the cyst and this was discharging liberally grayish, puttylike material. (A culture taken of this fluid was sterile after forty-eight hours' incubation.) The right round ligament and tube were secured at the fundus of the uterus, and the infundibulopelvic ligament was ligated and cut. The cyst was removed from the broad ligament. The broad ligament was peritonized. The infundibulopelvic and round ligaments were sewed to the fundus of the uterus. There were no peritoneal implants. The wound was closed in layers without drainage. The postoperative diagnosis was ruptured right dermoid cyst.

*Pathology.*—(Dr. Joseph Felsen). The specimen, a cyst, on gross examination, measured 9 by 7 cm. in size, apparently a resected ovary. The surface was diffusely hemorrhagic and presented several split pea sized, oval, yellow masses, which were firm in consistency. The wall measured 3 mm. in thickness. The cyst was multilocular, and the inner surface of the wall was studded with several papillary projections, which were pinkish in color and soft in consistency. The remainder of the lining presented many irregular yellowish raised areas. There was no gross evidence of sebaceous material or hair. Microscopically, the section showed a papilliferous cyst of the ovary. The slender connective tissue stalks were well vascularized, and the papillary projections were covered with simple columnar epithelium. There appeared to be no invasion of the stroma, but this tumor was capable of producing secondary implant of the peritoneum. One section revealed what appeared to be a thick-walled cyst containing cholesterol.

The *postoperative course* was uneventful. Rebound tenderness was present until the fourth day. The first four days the temperature varied between 100 and 101° F. and from then reached 100° F. daily, until discharge, except for a rise to 101° F. on the sixth and twelfth postoperative days.

The wound healed by primary union. Alternate sutures were removed on the sixth and the remainder on the eighth postoperative day. On the twelfth post-

# AN IMPROVED APPARATUS FOR TREATING ASPHYXIA OF THE NEWBORN INFANT

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AS ASPHYXIA is likely to occur in the delivery room, adequate equipment for resuscitation should be available and all doctors should be trained in the fundamentals of the treatment.

Obstetricians have more opportunity to prevent asphyxial deaths than has any other group in medicine. In their hands also rests the power to prevent many of the complications caused by asphyxia.

The method about to be described is simple, efficient and safe. In the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY* (20: 552, 1928), an apparatus for the resuscitation of asphyxiated newborn babies was described. This has now been improved and additions have been made which merit further consideration (Fig. 1).

The essentials of successful treatment of asphyxia neonatorum are the following: (1) Maintenance of body temperature, (2) correctness of posture to sustain an open airway, (3) provision of clear air passages, and (4) supply of oxygen to the lungs. This apparatus fulfills all these essentials in one compact unit.

Body heat is maintained by the electrically heated bassinet. The correct posture is obtained by adjusting the tilting platform on which the baby is placed. Clear air passages are a prerequisite to any satisfactory method of artificial respiration. The mucous membrane of the pharynx and trachea is delicate; therefore it is necessary that any suction be controlled and not be strong enough to cause injury. Gentle, but effective aspiration is accomplished by an electrically driven aspirator with an adjustable amount of negative pressure.

Oxygen is supplied to the lungs intermittently at carefully controlled predetermined pressures. This pressure may be regulated up to 16 mm. Hg, and it is indicated at all times by means of a water manometer gauge, which also acts as a water safety valve and makes it impossible to apply too great a pressure. The rhythm is controlled by the operator.

A face mask of "latex" rubber is designed to fit over the nose and mouth, and at its smaller end an aperture is provided for admitting the gas. On the inside of the face mask is attached a stiffly flexible rubber airway, or breathing tube, which extends over the tongue into the pharynx. The face mask is so designed that, while applied, there is no interference with the baby's inspirational efforts.

Once the baby has started breathing, the resuscitation mask should be replaced with the continuous flow inhaler. Oxygen in volume set by the flowmeter passes to the patient at a pressure that does not interfere with inspiratory or expiratory effort. There are no valves and bags to get out of order, or to interfere with respiration.

Failure to breath at birth may be due to any of several causes: asphyxiation, prematurity, brain hemorrhage, drugs, etc., and it is not always possible immediately to determine the cause. It will be seen, then, that to hold the baby head down is exactly the wrong position in the event that one is dealing with a brain hemorrhage.

Therefore, as soon as possible, the baby, carefully watched, should be placed in the heated bassinet in a fifteen degree Trendelenburg posture, with the head slightly hyperextended. Maintenance of body temperature is of vital importance. Not only is it of importance in the treatment of shock which may be present, but also it is of importance in the prevention of shock. Tissues take up oxygen more readily if the temperature is normal, or nearly so. Newborn babies always should be kept warm. The shock in itself tends to lower the blood pressure and resistance and, if not prevented or corrected, may be a potent factor in the production of fatal asphyxia.

breathing and mucous râles over both lung fields anteriorly and posteriorly, with impaired resonance. The impression received from the patient's recent history and from examination was toxemia of pregnancy with possible incipient edema of the lungs.

The patient went into labor and after ten hours of labor was delivered by low forceps. During the first stage of labor she coughed considerably and had difficulty in breathing when lying down. Under gas anesthesia in the second stage, she became cyanotic and the dyspnea was marked. In the Trendelenburg position, a large amount of yellow, frothy, sanguineous fluid ran from the mouth. Delivery was without obstetric complication. The patient left the delivery room in fair condition. A few moist râles could be heard over the entire chest.

Eight hours after delivery the patient was complaining of pain in the chest and was expectorating large amounts of bloody mucus. Two hours later I examined her and found all of the cardinal symptoms of acute pulmonary edema. She was in great distress. Treatment with the oxygen tent was started immediately. Dyspnea, cyanosis, rapid, weak pulse, and rapid, shallow respiration continued. Coarse râles and ronchi were present throughout the chest; the only aeration that was taking place was in the anterior chest as the patient lay in the prone position.

It was felt that the pulmonary edema was not entirely of cardiac origin and that the obvious cardiac strain might be partially or wholly relieved if normal oxygenation of the blood could be restored. Clearly, the oxygen that was being administered was not reaching the lungs by reason of bronchial obstruction, and death was impending. Realization that the cause of obstruction was not a fixed body but a fluid, which should be removable, brought me to the thought of aspiration through the bronchoscope as an immediate life-saving measure. The hope was felt that in the time thus gained the forces of nature, aided by the usual therapeutic measures, might prevail over the toxemia and the allied propensity to edema formation. Without further delay bronchoscopy was performed. An 8-mm. bronchoscope was used, with oxygen in the side-carrier.

Endoscopic examination showed the mucous membrane of the bronchi to be reddened and much swollen, so that definite diminution in the size of the lumen was produced. Larynx, trachea, and bronchi contained a large accumulation of thin serosanguineous secretions. The material in the larynx and trachea was frothy. On forced expiration secretions were seen issuing from the orifices of all the major bronchi. Approximately 60 c.c. of fluid was aspirated.

Improvement was almost immediate. The heart rate fell, showing relief of the cardiac strain, just as we had hoped; there was a drop in the respiratory rate and the cyanosis disappeared. The patient said that she felt much more comfortable.

The patient was relatively free of symptoms for about twelve hours, after which she began again to complain of respiratory difficulty, which increased very rapidly and became so severe that she herself asked to have the bronchoscopic treatment repeated. There was some rattling in the chest and the heart rate was increased. The bronchoscopy was repeated and a large quantity of secretion aspirated, but less than on the first occasion. The fluid was more viscid in character. The greater amount was obtained from the left lower lobe. The respiratory and heart rates fell promptly and from this time on recovery was smooth and spectacular.

The patient was discharged July 9, 1938, fourteen days after admission, well of the pulmonary edema. She was examined in December of the same year; no evidences of cardiac decompensation were then present.

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time the inflations to coincide with them. This timing can be done only by an apparatus whose rhythm is controlled by hand operation.

When breathing is established, but oxygen is still needed, remove the face mask with the attached airway, place the continuous flow face mask over the mouth and nose and set the flowmeter at four liters a minute.

In asphyxia of moderate degree the face mask with the attached airway should be used. It is not necessary to intubate the trachea in these cases and to do so may be difficult; it may even prove harmful. In profound asphyxia with a relaxed larynx, tracheal catheterization may be done without the same dangers of injury to the larynx and trachea. Provision is made for the attachment of a tracheal catheter in place of the face mask.

Tracheal catheterization is best achieved by direct vision with a laryngoscope but should be practiced only by those experienced in the procedure. It should be executed rapidly, for there is no time to lose in treating profound asphyxia.

Efforts at resuscitation must always be continued. Often babies will improve in color and heart action, but they may not breathe spontaneously for a long period of time. Chemical changes have taken place and it is necessary to reverse these changes. Then too, time is necessary for the elimination of drugs which may have been given the mother.

Progression of asphyxia may proceed with extreme rapidity. The oxygen reserve in an adult is about 600 c.c., which is not sufficient to sustain life for much over two minutes. Asphyxial collapse follows with appalling suddenness. The oxygen reserve in newborn babies is probably relatively smaller than that of an adult, so that the danger from asphyxia is correspondingly greater.

Time is of utmost importance in the treatment of asphyxia. It is easy to correct mild asphyxia and difficult to correct asphyxia when it becomes profound.

Asphyxia is a chemical phenomenon. To stimulate a failing heart when there is no oxygen in the blood stream, is useless. Supply oxygen and the heart will take care of the circulation. Both the circulation and the respiration are controlled by the gaseous exchanges.

For twelve years, in many hospitals, a similar apparatus has been successfully used. But the new model has the addition of three innovations: a heated bassinet, an aspirator, and a continuous flow of oxygen. With these additions all the requisites for resuscitation are combined in one unit.

The apparatus here described is manufactured by the Heidbrink Division of the Ohio Chemical Co., Cleveland, Ohio.

## A SATISFACTORY CORD CLAMP

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THE introduction of various types of cord clamps during the past few years is evidence that the use of cord ligation has gradually decreased. The reason for this is the added protection against hemorrhage and the ease of application.

The clamp here presented is a modification of the Hoffman clamp which is universally used for controlling the rate of flow in intravenous infusions. It was especially constructed by the Engineering Department of the New York Hospital and is made of monel and duraluminum metal, so that its total weight is 20 Gm. A photograph of the opened clamp and its application to the cord are shown in Fig. 1. The compressing action is obtained by a small spring (*a*) on either side. These give uniform tension throughout the range of use and length of jaw. The clamp is opened by turning the thumb screw (*b*) clockwise. This action separates the two crossbars. The outer bar is then opened, as shown in the photograph. It is then placed around the cord and the bar snapped into position. The clamp is adjusted to its proper position, which is about  $\frac{1}{4}$  inch above the skin margin. The thumb screw (*b*) is then released its full distance to point *c*, thus compressing the

The pharynx should be cleared at once with the aspirator, and if the baby does not breathe spontaneously, or if it is cyanosed or pale, oxygen should be given immediately.

A common error is waiting to see what will happen. Do not wait, for it is well known that the brain does not tolerate a deprivation of oxygen very long. Anoxia is the greatest factor in the mortality at birth and during the first few days of life. The morbidity due to anoxia cannot even be estimated. It is greater than is generally believed. Supply oxygen to the tissues immediately. No harm can be done by so doing, but delay may be fatal or may result in irreparable damage to the central nervous system.

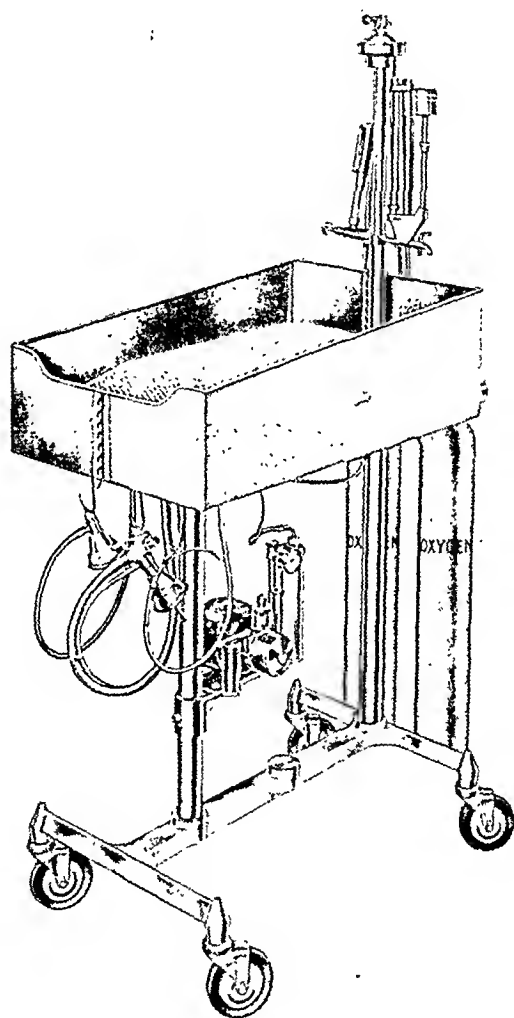


Fig. 1.

The oxygen should be supplied with the resuscitator by placing the mask over the nose and mouth with the airway over the tongue and the chin held up. Depress the lever on the mask and hold it down long enough for the lungs to be inflated. Then release the lever and the lungs will deflate because of their own elasticity. The lever should be held down for a few seconds each time, for it is then that the oxygen is taken up by the blood stream. The rhythm should be about twelve inflations a minute.

In deeply asphyxiated babies, respiration will begin usually with spasmodic inspiratory efforts, which do not take in air. Watch these efforts carefully and

## SPINELLI OPERATION FOR CHRONIC INVERSION OF THE UTERUS\*

FOLLOWED BY A FULL-TERM DELIVERY WITHOUT COMPLICATIONS

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(From The Gynecological Service, Cooper Hospital)

WE PRESENT this case report primarily because successful pregnancy and delivery of a full-term baby following the Spinelli operation for inversion of the uterus is very rare, and secondarily because chronic inversion of the uterus is not common.

The patient was a young woman who, at 18 years of age, was delivered at home of her first baby. The labor was long, difficult, and terminated by forceps. The placenta was delivered easily by the Credè method with no undue pressure or traction on the cord; however, there was profuse post-partum hemorrhage and shock. The inversion was not recognized, so that no attempt at reduction was made and no packing used. The patient reacted well from shock, but her convalescence was very stormy with greatly increased lochia, chills, fever, and lower abdominal soreness. She was permitted to get out of bed in four weeks and on the second day out of bed had a profuse hemorrhage with lower abdominal pain and was forced to return to bed. Chills and fever continued for four weeks more when she was admitted to the Gynecologic Ward of Cooper Hospital.

On admission she was pale and septic in appearance; her temperature was 101° F. and pulse rate 100. The blood count showed 55 per cent hemoglobin; 2,650,000 red blood cells, and 11,400 white blood cells. She was tender over the lower abdomen, but there was no distention or palpable masses.

Vaginal examination revealed a lacerated perineum and a smooth, firm mass which proved to be the inverted fundus of the uterus. The cervix was tightly contracted about this mass. There was some tenderness in the pelvis but no other palpable masses. A careful, but unsuccessful, attempt was made to replace the uterus.

On the following day she had a severe chill. Her temperature rose to 104° F. and pulse rate to 130. We felt that this resulted from the attempted reduction. The elevation of temperature gradually subsided, reaching normal at the end of one week.

Eight days later a second examination was made and involution found to be complete. Her condition was improved sufficiently so that reduction by the Spinelli operation was decided upon. This was done in the usual manner. It was found necessary to incise the entire anterior uterine wall before reduction could be accomplished. To close the uterus after reduction, a large wedge-shaped piece of the uterine wall had to be removed. Two layers of No. 2 chromic catgut were used in the closure. A small drainage tube was placed in the posterior cul-de-sac.

Her convalescence was satisfactory, although her temperature reached 101° F. for about five days. She was discharged three weeks after the operation in good condition.

Her menstrual periods were regular and painless until three years later when she became pregnant. The pregnancy progressed normally to term when she delivered, spontaneously, a living baby after a short labor. The puerperium was normal and she was out of bed on the tenth day. Five years later, eight years after the operation, she again became pregnant but had a premature labor at about the fifth month. Her convalescence was normal.

\*Presented at a meeting of the Philadelphia Obstetrical Society, December 7, 1939.

cord between the two bars as shown in the drawing. The cord is then cut close to the clamp. It is essential that the thumb screw be released the full distance by turning counterclockwise, so that the full action of the compression springs is obtained with the shrinkage of the cord. As the thumb screw is being released and the crossbars approximate each other, the pin (*d*) pierces the opening (*e*) and thereby automatically locks the clamp so that it cannot be accidentally opened. The clamp can be removed by turning the thumb screw (*b*) clockwise, thus separating the cross-bars.

The clamp measures  $1 \times 1\frac{1}{4}$  inches and the crossbars are  $\frac{3}{8}$  inch wide, thus eliminating the danger of cutting through the cord. The bars are ridged so that the outer peritoneal layer of the cord is perforated. This facilitates the escape of "Wharton's jelly." The compression spring cannot hurt the baby, since the coils separate as the clamp tightens.

The clamp is sterilized by boiling with the other instruments just before delivery. It has been our custom to remove the clamps at 8:00 A.M. on the following morning, which is the time of the first bath for the babies. Consequently the clamps remain in place from a minimum of eight hours to a possible maximum of thirty-two hours.

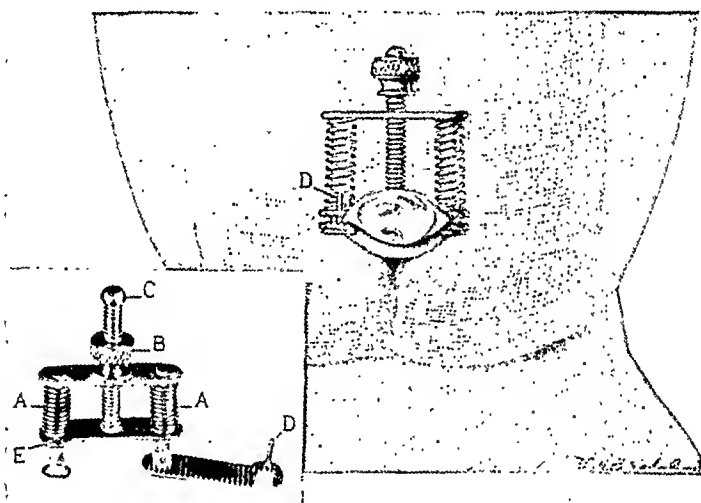


Fig. 1.—Showing clamp and its application to the cord.

No difference in results has been noted and the routine is a convenient one for the nursing staff. At the time of its removal, the compressed portion of the cord is of tissue paper thickness, and this portion is cut off with scissors, leaving only a small portion of the cord to be sloughed off.

The first 1,122 cases have been analyzed. These cases were studied between Nov. 24, 1937, and March 30, 1939. In 772 of these the cord was off at the time of discharge. In only 88 of this group did the cord fall off after the tenth day. In other words, in 67.85 per cent of the cases the babies were discharged with the cords off, and in 11.5 per cent of these the cords were off after the tenth day. In a similar series of 506 cases in which cord ties had been used, 286 babies, or 56.72 per cent, were discharged with cords off. In 23 per cent, or 66 cases, of this group, the cords were off after the tenth day. Thus, the clamp definitely decreases the period necessary for sloughing of the cord.

Of greater importance is the prevention of hemorrhage. In none of the cases was there any bleeding either before or after the clamps were removed. At the beginning of the period when the clamps were employed, it was noticed that in a few cases the clamps fell off after a few hours. However, this was due to lack of experience in that the thumb screw had not been completely released, thereby preventing closure of the clamp.

The amount of care necessary is greatly reduced, since the small portion of the cord remaining is completely dehydrated and necrosed. No further attention is necessary. The skin margins grow inwardly very rapidly.

once. This she failed to do. Ten days later, she had a profuse bleeding, following a jolting she received while alighting from a streetcar. She was admitted to the hospital shortly thereafter, with moderate bleeding from the vagina.

The following morning, June 26, on bimanual examination under ether anesthesia, a pear-shaped mass palpable in the vagina, with its lower portion presenting at the introitus, was found. This mass blended into the vaginal wall on its sides and upper limits. The fundus was not felt in its usual location, but instead a smaller portion, flush with the vaginal vault, was palpated. The mass had a friable, bleeding outer covering. The cervix could not be identified as such. Diagnosis of uterine inversion was made and the patient was returned to the ward. Treatment was instituted to overcome infection of the endometrium and severe secondary anemia.

On July 8, 1938, a Spinelli operation was done.

This case was one of complete inversion, there being no cervical cuff present and some difficulty was encountered in determining the proper level for incision in the anterior vaginal wall. The postoperative course was satisfactory, though there was considerable temperature elevation for the first three days following the operation. No drainage was used, but a tight tampon was employed. The patient was discharged on the fourteenth day and returned for follow-up examination Aug. 19, 1938, forty-two days after operation, complaining of some mucous discharge. The anatomic result was excellent.

900 SEVENTEENTH STREET, N. W.

## ANTERIOR PITUITARY TEST FOR EARLY PREGNANCY

HENRY G. HADLEY, M.D., WASHINGTON, D. C.

IN THIS test<sup>1</sup> two minims of anterior pituitary-like sex hormone are injected intradermally. After waiting one-half hour the presence of a wheal was described as a negative result. If there is a slight reaction, it is observed another half hour before drawing any conclusion. Patients thirty years old or older were considered to have delayed reaction and those near the menopause reacted as late as three hours.

A series of fifty cases was tested, including ten known cases of pregnancy; twenty-five nonpregnant women and fifteen men. The results of these tests were approximately 80 per cent positive in both the pregnant and nonpregnant patients. There was no difference in the reaction of the cases of pregnancy in relation to age or duration of pregnancy. The different ages in the ten known cases of pregnancy were as follows: 18, 20, 21, 23, 23, 23, 24, 25, 28, and 31. The duration of the pregnancy in these ten was three persons, three months; two persons, five months; two persons, six months, and three persons, seven months.

### CONCLUSION

The local reaction to this anterior pituitary-like hormone is unsatisfactory as a test for pregnancy.

### REFERENCES

- (1) Gilfillen, G. C., and Gregg, W. K.: *AM. J. OBST. & GYNEC.* 32: 498, 1936.
- Gersh, Isadore: *Ibid.* 35: 301, 1938.
- Frank, Chas. W., and Wahrsinger, Philip B.: *Ibid.* 35: 303, 1938.

She was re-admitted to the hospital in 1936, twelve years after the operation, complaining of lower abdominal pain and irregular bleeding. She gave a history of having been in bed at home for two weeks with fever.

Vaginal examination revealed a slightly lacerated cervix; the uterus was anterior and movable and the left adnexa were enlarged and sensitive. Our impression was that she had a subsiding salpingitis. After eight days with a normal temperature, she was discharged, and we have had no report from her since that time.

Although we have had no experience with the Haultain operation, from the review of the literature on this subject it would seem that this operation is quicker, easier to do, and that it leaves the uterus in better condition for future childbearing. The Spinelli operation, on the other hand, would seem to be safer if there has been infection and provided the patient is advised that future babies should be delivered by cesarean section.

527 PENN STREET

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## INVERSION OF THE UTERUS\*

E. W. TITUS, M.D., AND C. H. HIXSON, M.D., WASHINGTON, D. C.

THE existing classifications of this accident in the recognized textbooks, present considerable variation and confusion. Generally speaking, they are based on etiology and time factors and upon whether or not the fundus has entirely passed through the cervix.

In view of such variations of opinion, we feel that the classification of uterine inversion needs clarification. Classifying them into acute or chronic, based upon the time elapsing, namely one month, after the occurrence of the accident is arbitrary and unsatisfactory. We believe a better method should be evolved and to accomplish this, we offer the following suggestions. From the etiologic viewpoint, two main types should be recognized: puerperal and nonpuerperal. The puerperal type is divided into acute, which includes those cases immediately following delivery; subacute, those patients in whom many hours, or days, have elapsed before treatment is instituted; and chronic, having been present for a longer time. Nonpuerperal (gynecologic) may be divided into oncogenetic, traumatic, and idiopathic. Oncogenetic are those cases resulting from the gradual traction of new growths. Traumatic would include those cases sustaining a sitting or standing fall, or any accident causing a sudden and extreme increase in intraabdominal pressure. Idiopathic are those where definite cause cannot be ascertained. A large proportion of these, especially in older women, is believed to be oncogenetic in origin, with the complete disappearance of evidence of the presence of previous newgrowths.

Depending upon the degree of inversion, the latter is either partial or complete.

The patient, a negro woman, 21 years of age, was delivered at full term four years previously. There had been no obstetric complications. Her menstrual function had been normal since her labor. The last menstruation began May 20, 1938 and lasted three days, her usual time. The patient was first seen in the Garfield Memorial Hospital Outpatient Department on June 10, 1938. History revealed that on May 27, 1938, several days after cessation of last menses, she fell down the stairs of her home, sliding down on her buttocks. Vaginal bleeding began immediately and continued irregularly until she was seen in the clinic. Pelvic examination was not done at this time, but the patient was given oxytocics and advised to remain in bed. Five days later, she returned to the clinic, bleeding still continuing. Pelvic examination at this time revealed a large soft mass presenting at the introitus. This mass was red and bleeding slightly. A diagnosis of pedunculated myoma or inverted uterus was made and she was advised to enter the hospital at

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\*Presented at a meeting of the Washington Gynecological Society, March 25, 1939.

The need for a record of the members of the various specialties is evident. Formerly each Board of Diplomates published its own lists, but now it is a satisfaction to announce the appearance of a general directory, which includes the names of over 14,000 Diplomates certified by the constituent Boards, together with the essential biographic data relative to their particular qualifications. This is the only official American Directory of its kind and includes in its almost 1,600 pages not only alphabetical and geographical lists, but the organization and examination requirements of each of the American Boards are explained in full. These features make the book unique and invaluable to all doctors, hospitals, social agencies, libraries and professional organizations, and its practical importance will become more evident as its circulation and employment become more widespread. The Board of Editors, under the able direction of Dr. Paul Titus, is to be commended for their labors in bringing to a successful conclusion this worthwhile undertaking.

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**Geiger and Burlingame: A Statistical Survey of 140 Cases of Gonorrheal Ophthalmia with Data of 68 Cases Treated with Nonspecific Protein (Typhoid Vaccine),** Am. J. Ophth. 21: 421, 1938.

From January, 1918 to July, 1937, 140 cases of gonorrheal ophthalmia were treated in the Isolation Hospital Division of the San Francisco Department of Health. Forty-nine of these cases were classified as ophthalmia neonatorum, and in all but three of them 2 per cent nitrate was stated to have been used at birth.

From 1918 to 1927, 51 patients were treated, 20 of whom had ophthalmia neonatorum. Only local treatment was used except in 4 patients when milk injections were tried without apparent results and then discontinued. Corneal ulcers occurred in 27 per cent of these cases despite the treatment.

From 1927 to 1937, there were 89 cases; 68 of the patients were treated with nonspecific protein therapy by the intravenous use of typhoid vaccine. Local treatment was considered sufficient for the other 21 cases, which were mild. The average duration of the disease was 3.6 days before any treatment was instituted. None of the 29 patients with ophthalmia neonatorum in this series developed corneal ulcers, although corneal ulcer as a complication occurred in 22 cases of the entire group. The average number of doses of typhoid vaccine given to each patient was 4.44; the least dosage in the number of organisms was 5,000,000 and the greatest number 250,000,000, given to one adult. Thirteen per cent of the group treated with nonspecific protein therapy developed corneal ulcers, in comparison with the 27 per cent of the first group.

J. P. GREENHILL.

**Ruther, H.: Spontaneous Rupture of the Umbilical Artery Before the Onset of Labor,** Arch. f. Gynäk. 168: 44, 1939.

The author reports a rather unusual accident of late pregnancy. The patient was a young primipara who began to bleed rather vigorously several hours before the onset of labor. There were no local vaginal findings, no placenta previa, and no premature separation of the placenta to account for this loss of blood. After a twenty-one-hour labor the patient delivered a full-term dead fetus. Examination of the placenta revealed the cause of the vaginal bleeding and of the fetal death. Spontaneous rupture of the umbilical artery just above the placental insertion of the umbilical cord was found. Histologic examination of the cord and the artery showed a local area of necrosis apparently due to malnutrition. The author calls attention to the fact that this type of accident can, even though very rarely, be the cause of prenatal bleeding.

RALPH A. REIS.

## Editorials

### The Lead Nipple Shield

SINCE Wilcox and Caffey,<sup>1</sup> in 1926, described two cases of lead encephalitis in nursing infants due to the use of lead nipple shields by the mother, a number of other cases have been reported.<sup>2-4</sup> A recent fatal case with a review of the literature was reported by Bass and Blumenthal.<sup>5</sup>

The therapeutic effect of lead nipple shields is due to lead lactate, formed by the action of milk on lead. Obstetric opinion has held that careful washing of the nipples before nursing eliminates any danger to the infant. However, large amounts of lead were recovered from the milk of a mother using these shields one week after nursing had been discontinued.<sup>5</sup> Thus it is obvious that lead is ingested by the infant.

In all cases reported the shields were used for a number of months. Whether the amount ingested when they are used for a few days only is harmful to the infant is open to question. Bass and Blumenthal believe that many cases of unexplained anemia, colic, and convulsions occurring later in infancy may be due to lead in the body.

Until recently lead nipple shields were obtainable without prescription at any drug store. The printed matter which accompanies them states that "they are in no way likely to be injurious to the infant." Their sale and use has now been forbidden in New York State. Recently the U. S. Department of Agriculture banned them to interstate commerce. However, since they may still be obtained in many states, it is important for physicians to be aware of this hazard to nursing infants.

Thus another custom, hallowed by time and tradition, seems on the way to be relegated to the accumulating mass of therapeutic disards.

*Katharine G. Dodge.*

### A Directory of Specialists\*

THE growth of the specialist practice of medicine in this country has brought with it certain problems none of which is of greater importance than the definition of a specialist and who may be designated as such. Various groups have been developed in recent years for providing formal certification of specialists, but the need for cooperative efforts to establish uniformity of procedure served to stimulate the formation of the general Advisory Board of Medical Specialists during 1933 and 1934. This Board has been expanded to include practically all of the recognized specialties in medicine and has developed close affiliations with medical schools and hospitals, examining boards and professional organizations.

<sup>1</sup>Wilcox, H. B., and Caffey, J. P.: J. A. M. A. 86: 1514, 1926.

<sup>2</sup>Findlay, Leonard: Post Graduate M. J. 11: 251, 1935.

<sup>3</sup>Rapaport, Milton and Kenney: J. A. M. A. 112: 2040, 1939.

<sup>4</sup>Mississippi Valley M. J. 61: 96.

<sup>5</sup>Bass, M. H., and Blumenthal, S.: J. Pediatr. 15: 724, 1939.

\*Directory of Medical Specialists Certified by American Boards. Columbia University Press, New York, 1940, 1573 pages.



# Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

## Review of New Books

### Gynecology

Fluhmann's monograph<sup>1</sup> is based on personal investigations of the pathology, diagnosis, and treatment of menstrual disorders. The author has a wide experience, both in the laboratory and clinic, and throughout emphasizes the needs of the clinician.

Every phase of the monthly cycle from both the normal and the abnormal aspects, are gone into with full evaluation of the investigative as well as the clinical literature. Fluhmann describes his own methods for detecting the gonadotropic as well as the estrogenic hormones in the blood and urine, and the results he has obtained from these bioassays. The pathology, diagnosis, and treatment of pathologic menstrual phenomena are clearly set forth. The therapy of these conditions is as yet in such a state of flux that differences of opinion as to the efficacy of various remedies suggested are both natural and understandable. The illustrations are excellent.

—R. T. Frank.

Seitz, in his *Wachstum, Geschlecht und Fortpflanzung*,<sup>2</sup> as always, shows originality in his viewpoint. This book, according to the author, has gradually developed from ideas which have crystallized and perhaps have lured him into producing a book before our knowledge really justifies such generalization.

The main ideas involved deal with why the feminine sex has been so preponderantly overburdened with cares of reproduction, as well as the peculiar growth phenomena in the female noted during pregnancy, after general body growth has ceased. Investigation directed to the morphologic changes touch merely upon the surface of the actual physicochemical alterations which are necessary in reproduction. The author distinguishes sharply between somatic and gametic cells. The functions of the sex cells, according to him, have nothing to do with the host but solely with the reproductive function. He discusses the sexual hormonal system, and emphasizes the role of the biocatalyzers under which hormones and vitamins are included. He then attempts a synthesis of the accumulated evidence on the entire subject. While the organism is built up purposefully, mistakes have occurred. He then enters into innumerable details which do not permit of review. He contrasts sharply the specificity of the proteins and the very opposite for the hormones, although apparently omitting the protein composition of insulin and the gonadotropic hormones. Another sharp contrast is that the vitamins are obtained from plant food while the hormones are developed from body cells.

Although this book, because of the present state of our knowledge, is necessarily sketchy in many spots, it contains a huge amount of information viewed from the most interesting and important aspect.

—R. T. Frank.

<sup>1</sup>Menstrual Disorders. Pathology, Diagnosis and Treatment. By C. Frederic Fluhmann, Associate Professor of Obstetrics and Gynecology, Stanford University, School of Medicine, San Francisco, etc. 119 illustrations, 329 pages. W. B. Saunders Company, Philadelphia, 1939.

<sup>2</sup>Wachstum, Geschlecht und Fortpflanzung, als ganzheitliches, erbmaessig-hormonales Problem. Von Professor Dr. Ludwig Seitz. With 125 illustrations, including some in colors, 410 pages. Verlag von Julius Springer, Berlin, 1939.

# Society Transactions

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## NEW YORK OBSTETRICAL SOCIETY

*MEETING OF NOVEMBER 14, 1939*

The following papers were presented:

**Plastic Reconstruction of the Urethra.** Dr. Samuel H. Geist. (For original article, see page 843.)

**A Study of Selected Cases of Morbidity on the Obstetrical Servical of Bellevue Hospital for the Year 1939.** Dr. George L. Bowen (By invitation).

**Transcervical Cesarean Section With Bladder Mobilization and Peritoneal Exclusion.** Dr. Erwin F. Smith (By invitation). (For original article, see page 763.)

*MEETING OF DECEMBER 12, 1939*

The following papers were presented:

**The Assay of Posterior Pituitary Extract (Pitocin) Upon the Pregnant Human Uterus With the Lorand Tocograph.** Dr. Douglas P. Murphy (by invitation). (For original article, see page 808.)

**Some Endocrine Studies in Abnormalities of the Menstrual Cycle and in Sterility.** Dr. J. S. L. Browne (by invitation).

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## OBSTETRICAL SOCIETY OF PHILADELPHIA

*MEETING OF DECEMBER 7, 1939*

The following papers were presented:

**Curettage; Pregnancy Hydramnion.** Dr. James S. Raudenbush.

**Spinelli Operation for Chronic Inversion of the Uterus.** Dr. Gordon F. West. (For original article, see page 892.)

**The Advantages of the Vaginal Approach to Pelvic Pathology.** Dr. Leonard Averett. (For original article, see page 776.)

**The Assay of Posterior Pituitary Extract (Pitocin) Upon the Pregnant Human Uterus With the Lorand Tocograph.** Dr. Douglas P. Murphy. (For original article, see page 808.)

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## CHICAGO GYNECOLOGICAL SOCIETY

*MEETING OF NOVEMBER 17, 1939*

The following papers were presented:

**Closure and Subsequent Care in Obstetric and Gynecologic Abdominal Wound Disruption.** Drs. H. C. Hesseltine and George Bohlender (by invitation).

**Decidualike Changes in the Endometrium without Pregnancy.** Drs. Richard W. Telinde and Erle Henriksen (by invitation). (For original article, see page 733.)

**Ectopic Decidua in the Vermiform Appendix.** Drs. Ralph A. Reis and Melvin B. Sinykin. (For original article, see page 870.)

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## BROOKLYN GYNECOLOGICAL SOCIETY

*MEETING OF DECEMBER 1, 1939*

The following paper was presented:

**Regional Iritis as a Problem in Pelvic Diagnosis.** Drs. Charles A. Gordon and Alex. H. Rosenthal. (For original article, see page 846.)

the woman's body significantly different from that of the male on account of her part in the propagation of the species, and feels that in general, backaches are largely an orthostatic symptom or complex. This is a very thorough consideration of a frequent complaint and finding in women, and should be of interest not only to gynecologists but to orthopedists as well.

—Philip F. Williams.

This small book, *Cancer of the Breast and Cancer of the Uterus*,<sup>6</sup> is a recapitulation of the author's personal observations on cancer supplemented by abstracts and illustrations from many articles which have appeared in various medical journals, together with the voiced opinions of a great many radiologists and surgeons whom she has consulted with reference to problems of her practice. She offers the volume as a method by which the general practitioner can become familiar with the appearances and symptoms of cancer of the breast and cancer of the uterus, which may be encountered in daily work. There is a very short discussion of the use of radium in cancer of the uterus.

—Philip F. Williams.

Sommer, from the Leipzig Woman's Clinic, presents this textbook, *Die Gonorrhoe der Frau*,<sup>7</sup> for the practicing physician. He discusses the social significance of gonorrhea, its relationship to reproduction, the functional changes which it causes in the pelvic organs, and the various modes of therapy. The subject matter of the text is arranged in a conventional manner, bringing out the etiology, bacteriology, and general pathology of this infection. He discusses the various infections, means of diagnosis, and treatment. He holds the complement fixation test of little value and bases the diagnosis on clinical examination supplemented by smears, and in chronic cases provocation appearances. He is conservative in suggesting operative therapy of gonorrhea in the upper pelvic organs, and discusses the limitations of roentgen therapy. Influence of gonococcal infections on reproduction, and their part in the morbidity of pregnancy, parturition, and the puerperium are thoroughly described. After an excellent chapter on gonorrhea of the newborn and the infant, he deals with the remote complications of this infection. In conclusion, he lays great stress on the public health aspects and the prophylaxis of this infection in its relation to the general social welfare of the community.

—Philip F. Williams.

## Obstetrics

The separate handbooks on maternal care and maternal care complications, which have been previously reviewed in this JOURNAL, form the present conjoint volume issued by the American Committee on Maternal Welfare.<sup>8</sup> This volume deserves a widespread circulation among general practitioners, hospital interns, and public health nurses on account of the direct and concise approach to the problems presented.

—Philip F. Williams.

This *Textbook of Obstetrics*,<sup>9</sup> by Dr. Reed and Miss Cooley, is an excellent presentation on the subject of obstetrics for the nurse. The authors have given the essential principles of obstetrics as regards anatomy, physiology, and pathology in the manner of the usual major textbooks. They have written into the text suggestions for the nursing care of various normal and abnormal conditions and processes

<sup>6</sup>*Cancer of the Breast and Cancer of the Uterus*. By Marian Ellsworth Anderson, M.D., Clinton, Ohio. Franklin Press, Clinton, Ohio, 1939.

<sup>7</sup>*Die Gonorrhoe der Frau*. Von Dr. Karlheinz Sommer, Marinestabsarzt, Universitäts-Frauenklinik in Leipzig. With 47 illustrations and 185 pages. Verlag von Georg Thieme, Leipzig, 1939.

<sup>8</sup>*Maternal Care and Some Complications*. Edited by Dr. F. L. Adair, approved by American Committee on Maternal Welfare, Inc. University of Chicago Press, Chicago, 1939. 194 pages.

<sup>9</sup>*A Textbook of Obstetrics, with special reference to nursing care*. By Charles B. Reed, Associate Professor of Obstetrics, Northwestern University Medical School, etc., and Bess I. Cooley, R.N., Supervisor and Instructor, Department of Obstetrics, Wesley Memorial Hospital, Chicago. With 209 illustrations, 476 pages. The C. V. Mosby Company, St. Louis, 1939.

From the antipodes, a student textbook has appeared on the subject of *Gynaecology*<sup>3</sup> from the pen of Herbert H. Schlink of the University of Sydney. The author states that he has been influenced largely by a series of textbooks which have appeared in England, Germany, and the United States. The subjects have been so arranged that only thirteen chapters were found necessary, of which the last three include examination of the patient, operative gynecology, and postoperative complications.

In the main, the English influence predominates, as seen by the emphasis placed on examination of virgins and nervous patients under anesthesia, the use of the Manchester operation for prolapse, etc. The standpoint in inflammatory diseases is conservative although the author mentions that particularly in working women, in whom time for restoration to full function is essential, operative intervention should be preferred to palliative treatment. This book is adequate in every way for study by medical students.

—R. T. Frank.

*Sterility and Impaired Fertility*<sup>4</sup> by four authors, with a foreword by Lord Horder, covers these subjects from every aspect. It presents the most recent view of our English colleagues. Apparently this is the first monograph on the subject published in England.

The authors emphasize that the high percentage of childless marriages is not due to contraception. According to their view point, one year should suffice for conception and according to the authors, “. . . within certain limits, the chances of fecundation vary directly with the frequency of coitus.” Not every worker in the field will agree with these two viewpoints. In preparing this book, all sources have been liberally consulted. A very careful and well-illustrated analysis of sperma assay is presented. Operations for male sterility, without going into too great technical details, are presented. In the investigation of the female, the Rubin insufflation test as well as the lipiodol and hysterosalpingography are accorded equal importance. Such diverse phases as hormone assay, “hormone therapy,” operations for re-opening the tubes are taken up.

So much ground is covered in this volume that little more than an epitome of the subject could be presented. It is well written, well illustrated, well authenticated, and informative.

—R. T. Frank.

This book, *Die Kreuzschmerzen der Frau*<sup>5</sup> by Martius, discusses the significance and treatment of the various back pains to which women are subject. It is interesting to note that in a series of 200 women he interviewed, Martius states that somewhat less than one-third voluntarily complained of various backaches, more than one-third acknowledged such symptoms when questioned, and exactly one-third declared themselves free from such conditions.

Martius considers the various etiologic factors in the production of the back pains from the standpoint of the pelvic organs, displacements, endometriosis, infections, and tumors. He brings out the relationship of these diseases to back pains. He then proceeds to the consideration of the posture and physical constitutions of the women who complain of such conditions, developing his thesis from the orthopedic standpoint. He brings out in this section the various diseases of the spinal column, and spinal and pelvic joints, stressing the importance of properly performed roentgen ray examinations. He regards the architecture of

<sup>3</sup>*Gynaecology*. By Herbert H. Schlink. Lecturer and Examiner in Gynaecology, University of Sydney, etc. 179 illustrations. 557 pages. Angus and Robertson Limited, Sydney, 1939.

<sup>4</sup>*Sterility and Impaired Fertility*. By Cedric Lane-Roberts, Gynecological Surgeon, Royal Northern Hospital, Albert Sharman, Assistant Surgeon, Royal Samaritan Hospital in Glasgow, Kenneth Walker, Surgeon to Genito-Urinary Department, Royal Northern Hospital, and B. P. Wiesner, Consulting Biologist, Royal Northern Hospital. Illustrated, 419 pages. Paul B. Hoeber, Inc., New York, 1939.

<sup>5</sup>*Die Kreuzschmerzen der Frau. Ihre Deutung und Behandlung, Gynaekologische Orthopaedie*. Von Professor Dr. Heinrich Martius, Direktor der Universitaets-Frauenklinik in Goettingen. With 64 illustrations and 179 pages. Verlag von Georg Thieme, Leipzig, 1939.

specialty. There is an admirable collection of source material for the student of obstetric history who may wish to work further in this always interesting field. Dr. Findley is to be congratulated on his contributions to the history of obstetrics.

—Philip F. Williams.

Kehrer presents a clear and concise survey of all available information on the complex and important problem of *Intracranial Hemorrhages of the Newborn*.<sup>13</sup> Though not offering any particularly new findings, this small monograph, systematically arranged, excellently illustrated and well written, will be welcomed by obstetricians and practitioners. The author discusses authoritatively all the various aspects of these injuries, their frequency, anatomic characteristics, etiologic factors especially those of a mechanical nature, clinical diagnosis, treatment, prophylaxis and their immediate and remote prognoses. The volume closes with an extensive and useful bibliographic list.

In regard to the prevention of intracranial birth injuries Kehrer refers to the obvious contradictions in expressed views, some writers advocating wider use of the forceps, others denouncing its prevalent misuse, while others again favor cesarean sections. Realizing the danger in exaggerated conservatism as well as in ready resort to operative interference, the author attempts to tabulate directions toward "possible" prevention of such damages. However, in the last analysis, prevention in the individual case depends chiefly on the good judgment and skill of the attending physician—not on strict observance of definite rules.

—Hugo Ehrenfest.

This pamphlet, *Baptism of the Infant and Fetus*<sup>14</sup> discusses for the physician, the teachings of the Roman Catholic Church in relation to the baptism of the infant and the fetus. Specifically, it describes what should be done by the physician or nurse in the case of impending fetal death during or after delivery where the parents are of the Roman Catholic faith. The subject of post-mortem cesarean section is also discussed. As many physicians and nurses in general hospitals are unaware of the religious rites enumerated here, it would seem advisable for a copy of this small pamphlet to be available in or about the delivery room suite of all hospitals.

—Philip F. Williams.

## Endocrinology

Goldzieher's *The Endocrine Glands*,<sup>15</sup> in some respects, is an important contribution to the subject. This volume of 916 pages in rather small print contains a huge amount of material which is quite impossible to review in detail. It is based on a large personal experience and is basically sound on the anatomy and physiology of the subject. The description of the syndromes likewise is excellent. Each individual subject is concluded with a well-selected bibliography. It is to be regretted that no authors' index is appended, as the many references are difficult to find because of their scattering and wide distribution. The 271 illustrations are selected with care and judgment, showing unusual and rare conditions.

The author is extremely optimistic as to the effects of therapy. He "has obtained uniformly good results with anterior lobe extract made by . . . Co." He states that "Oral administration of pituitary substance is frowned upon by the spokesmen of 'organized medicine,' but the reason why their verdict does not seem acceptable, has been discussed before." His extreme faith in therapeutic

<sup>13</sup>Die Intrakraniellen Blutungen bei Neugeborenen. Von Professor Dr. Erwin Kehrer. Direktor der Universitäts-Frauenklinik in Marburg. With 20 illustrations including 2 colored illustrations and 1 table, 79 pages. Verlag von Ferdinand Enke, Stuttgart, 1939.

<sup>14</sup>Baptism of the Infant and the Fetus. An Outline for the Use of Doctors and Nurses. The Fourth Edition by the Rev. J. R. Bowen, Chaplain, St. Joseph Mercy Hospital, Dubuque, Iowa. The M. J. Knippel Co., Dubuque, Iowa.

<sup>15</sup>The Endocrine Glands. By Max A. Goldzieher, Endocrinologist, Gouverneur Hospital and Brooklyn Women's Hospital, New York, etc. Illustrated with 271 figures, 916 pages. D. Appleton-Century Company, New York, 1939.

in order that the nurse may realize her place, duty and responsibility throughout pregnancy, labor, and the puerperium. There are excellent chapters on the newborn child and its nursing care. The manner of presentation and the subject matter should make this book of especial value to the nurse who expects to make maternity practice a large part of her work.

—Philip F. Williams.

Herbert Albers offers an exhaustive discussion of the *Normal and Pathologic Physiology of the Water Metabolism of Pregnant Women*.<sup>10</sup> The material is arranged in the following order: The Importance of Water for Organic Life; Blood and Plasma Volume During Pregnancy and Their Relations to Pregnancy Edema; Venous Pressure During Normal Pregnancy, in Pregnancy Toxioses and During Labor; Dependence of Colloid-Osmotic Pressure Upon the Serum Protein Situation in Normal and Toxic Pregnancy and During the Puerperium. Answers are given to three questions: Is the vascular system more permeable for fluids and plasma during pregnancy? (Yes); Based on the facts given in preceding sections of the monograph, can the water metabolism of normal and edematous gestational periods be explained? (Yes); What is the practical significance of these findings? (Vascular permeability is increased in about 90 per cent of all pregnancies, but this cannot be changed therapeutically because neither oral nor intravenous administration of calcium ever raises the calcium contents of the blood during pregnancy. We cannot alter the reduced water binding ability of albumin especially in marked instances of edema. It is possible to reduce the essentially increased venous pressure, particularly during labor.)

By means of extended experimental investigations, the author has revealed many new and valuable facts in regard to the water metabolism during pregnancy, both under physiologic and pathologic conditions. Tables, diagrams, a complete bibliography, and an index greatly enhance the value and usefulness of this monograph.

—Hugo Ehrenfest.

Having previously presented a thorough discussion of vitamins A and C, Gaethgens in this new monograph deals exhaustively with the *Significance of Aneurin (Vitamin B<sub>1</sub>) in Pregnancy and the Puerperium*.<sup>11</sup> On the basis of findings recorded in literature but particularly as a result of his own extensive studies, the author arrives at various conclusions of which we shall quote but one: Pregnancy and puerperium do not increase the daily requirements for vitamin B<sub>1</sub> intake. If resorption from the gastrointestinal canal is normal, there is for normal pregnant women no need for changes in diet or for administration of vitamin B<sub>1</sub>.

—Hugo Ehrenfest.

Dr. Palmer Findley in his *Priests of Lucina*<sup>12</sup> presents in his usual delightful style, a panorama of obstetrics from times immemorial to the present era. Standing out against the background of medicine through ancient, medieval, and modern times, he has outlined for us the ebb and flow of the superstition and mysticism of obstetrics gradually growing clearer through writings of the Greeks and Romans, the authors of the Middle Ages and culminating in the Modern Era of hospitals, aseptic delivery and present humanities of obstetrics. The outstanding figures of obstetrics have been well chosen for individual biographic reference, and all the names signalize the development of some forward step in practice. Of especial interest, are the five chapters on the special phases of obstetrics where again the influence of one individual or another has stood out strongly, connecting his name forever with some particular aspect of our

<sup>10</sup>*Normale und Pathologische Physiologie im Wasserhaushalt der Schwangeren.* Von Herbert Albers in Leipzig. With 25 illustrations and 119 pages. Georg Thieme, Leipzig, 1939.

<sup>11</sup>*Der Aneurin (Vitamin B<sub>1</sub>) Haushalt in der Schwangerschaft und im Wochenbett.* Von Dr. Gerhard Gaethgens, Leipzig. With 7 illustrations and 76 pages. Verlag von Georg Thieme, Leipzig, 1939.

<sup>12</sup>*Priests of Lucina. The Story of Obstetrics.* By Palmer Findley, M.D. Illustrated, 421 pages. Little, Brown & Company, Boston, 1939.

In this monograph concerning *The Prevention of Hereditary Psychiatric tendencies*, Zurukzoglu<sup>19</sup> discusses the eugenic problems concerned, with particular reference to the recent laws regarding sterilization and castration in the Reich. He has called to his assistance quite a number of contributors who have developed various sections, such as the relationship of gynecology, technique of sterilization and castration, and a number of particular mental or nervous diseases which come under this general subject.

Wolf discusses particularly the psychiatric indications for castration, and Zurukzoglu concludes the text by bringing together the conclusions of the various contributors as well as a summarization of the practice of sterilization, not only in Germany but in the Scandinavian countries and other countries of Europe and abroad. It is interesting to note that as far back as the German Surgical Congress in 1935, 12,000 sterilizations for psychiatric reasons were reported, of which 42 per cent were done in feeble-minded people, 25 per cent in schizophrenics, and 13 per cent in epileptics. This very thorough consideration of hereditary tendencies should be of extreme interest to psychiatrists, or practitioners interested in prophylactic sterilization and castration.

—Philip F. Williams.

The authors have presented in this volume, *The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds*,<sup>20</sup> a summary of existing knowledge concerning the effect of such agents in the control of bacterial infection. As they state, the clinical application has far outstripped the knowledge of the fundamental mechanism of action of these new drugs. In the short six years since prontosil was first used, a truly enormous amount of literature on bacterial chemotherapy has been produced. For this reason a summarization of the subject is especially welcome.

The first chapter takes up the history of the therapeutic application of these compounds. Prontosil was evidently first used in July, 1935, in a case of meningitis. The second chapter discusses the chemotherapy of the bacterial infections. The authors discuss streptococcal, staphylococcal, pneumococcal, meningococcal, gonococcal, and typhoid and paratyphoid infections and a number of others in which little evidence has been found to suggest that this type of drug had any value in combatting an experimentally produced infection. Prophylactic use of such compounds in experimental infections is also discussed. The study of the toxic effects, pharmacologic standards, and the test that determines sulfanilamide or its derivatives in the body fluids comprises the third chapter. In a succeeding chapter the mode of action of such compounds is discussed at length. The authors state that so far one must be content with the simple conception that they inhibit growth of micro-organisms in the body and in the test tube. The mode of action of sulfur benzene derivatives remains inadequately explained.

In the four final chapters of the book, the authors critically review and survey the clinical use of sulfanilamide, sulfapyridine, and prontosil in a definite effort to evaluate their clinical applications in specific human pathologic processes. There is an excellent recapitulation of the use of sulfapyridine in lobar pneumonia. Colebrook's work on puerperal sepsis at Queen Charlotte's Hospital is commented on at length. Of special value is the chapter on Clinical Toxic Manifestations following the use of these compounds. Cyanosis, acidosis, temperature, dermatitis, and nervous disorders, as well as other complications, have been discussed, and the effects on the hematopoietic system are reviewed. The documentation is voluminous, and confirms the impression as one reads the book, that no important contribution on this subject has been overlooked.

<sup>19</sup>*Verhütung Erbkranken Nachwuchses. Eine kritische Betrachtung und Würdigung. Herausgegeben von Dr. St. Zurukzoglu. Privatdozent für Hygiene und Bakteriologie an der Universität Bern Basel 1928, Benno Schwabe & Co., Verlag.*

<sup>20</sup>*The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine, and Allied Compounds.* By Perrin H. Long, M.D., Associate Professor of Medicine, School of Medicine, Johns Hopkins University, etc., and Eleanor A. Bliss, Sc.D., Fellow in Medicine, Johns Hopkins University. 319 pages. The MacMillan Company, New York, 1939.

procedures is shown, for example, by the fact that he classifies the Laurence-Moon-Biedl syndrome as of pituitary origin "partly because of the improvement repeatedly obtained by pituitary therapy."

This book should prove of real value to obtain an insight into the origin, causes as well as description of the endocrine diseases, if the reader will interpret the therapy with sufficient eclectic discrimination.

—R. T. Frank.

Within a period of less than three years, a second edition of William Wolf's *Endocrinology in Modern Practice*<sup>16</sup> has appeared. Evidently this book has filled a definite want. The second edition, only fifty-eight pages longer than the previous one, has undergone extensive revision and appears to contain the advances up to about January, 1939. This must have been a difficult task, considering the rapid changes occurring in this popular subject.

To the revised edition have been added such newer acquirements as the discovery and the use of protamine zinc insulin; endometrial suction biopsies (which are well illustrated) but to which, in my opinion, too much importance is accorded; and a description of vitamins from A to K.

The previous form of the book has been preserved, the illustrations are excellent, well reproduced and well chosen. For the practitioner of experience, this book should prove interesting and instructive reading.

—R. T. Frank.

*The Endocrine Secretions of the Ovary*<sup>17</sup> by Carlos Colmeiro Laforet is the first Spanish book received since the end of the Civil War and is a welcome sign that Spain is returning toward normalcy. This monograph is a summary of the world literature, dealing with the subject and covering it with a fair degree of adequacy.

Throughout it is definitely colored by the author's opinions but contains no investigative contributions. It should prove useful to bring before the Spanish profession this important subject. Numerous inaccuracies, particularly in the names and references, are evident, which, however, do not seriously detract from the value of the monograph.

—R. T. Frank.

### Miscellaneous

*Congenital Malformations*,<sup>18</sup> by Douglas P. Murphy, is a study concerning the relative frequency of congenital defects in families already possessing one malformed member. The author discusses the method by which his material was obtained, and the questionnaire used. He shows the relative frequency of malformations in his study in Pennsylvania, and presents a discussion of the reproductive characteristics of the parents of defective children.

Dr. Murphy notes that malformations afflict white and negro in the ratio of 57 to 32. He has observed that the birth of a malformed child is usually preceded by a period of relative sterility, and that the malformed offspring is born prematurely more than four times as frequently as normally developed brothers and sisters. He found that approximately 40 per cent of the mothers of malformed children had diets insufficient in minerals and in vitamins. There was an unusual incidence of placenta previa, and some symptom of toxemia was present in almost one-third of the cases.

Murphy states that perhaps the single most convincing piece of evidence in favor of heredity is the frequent presence of defects in brothers and sisters, and that his data point to disturbances in the germ cell prior to fertilization as the factors responsible for maldevelopment.

—Philip F. Williams.

<sup>16</sup>*Endocrinology in Modern Practice*. By William Wolf, Endocrinologist to the French Hospital, etc. Second edition, completely revised. 176 illustrations, 1077 pages. W. B. Saunders Company, Philadelphia, 1939.

<sup>17</sup>*Las Increciones del Ovario*. Por Carlos Colmeiro Laforet, La Coruna. Liberia "Gali." Santiago de Compostela, Spain, 1939.

<sup>18</sup>*Congenital Malformations. A Study of Parental Characteristics*. With Special Reference to the Reproductive Process. By Douglas P. Murphy, M.D., F.A.C.S. With 55 tables, 7 graphs and 1 photograph.



In the volume under *Population, Race and Eugenics*,<sup>23</sup> Dr. Siegel discusses what may improve positive eugenics or impair negative eugenics for future racial qualities in a physical or mental sense. On the one hand, eugenics must concern itself with disease and on the other hand with the relationship of infertility or education and successes. The author discusses the facts upon which positive and negative eugenics depend. He points out serious defects in all trends of reproduction and as an example reminds us of the 50 per cent of educated women who do not marry. Comparison of fertility is discussed in view of birth control, late marriage, and economic status. To remedy the condition to which he calls attention, he discusses housing conditions, economic systems, extension of birth control in rural and industrial districts and the change of attitude toward marriage. The author devotes an interesting chapter to racial theories in relation to eugenics, portraying the known and assumed effect of various racial crossings.

The first half of the book ends with a chapter on Rational Marriage, and how it may be effective. The second half of the book is devoted to restrictive eugenics, mental disorders, feeble-mindedness and epilepsy and a discussion of the main restrictive measure, such as education, restrictive marriage laws, segregation, and sterilization. In regard to sterilization he states that the Compulsory Sterilization of 1933 in Germany was followed by well over 50,000 sterilizations in the first year. The author states that in California, only four known pregnancies followed sterilization and that there were three known failures of vasectomy in California. Among the other general conclusions, he states that a physician who in his prenatal practice has neglected to take a blood test of a mother who suffers from syphilis, and a child born with congenital syphilis, should be held liable for malpractice.

—Philip F. Williams.

After a lapse of twenty-seven years the story of Dr. Beaumont and Alexis St. Martin, *Life and Letters of Dr. William Beaumont*<sup>24</sup> by Dr. Myer, has reappeared in a new print. Sir William Osler's introduction to the first edition has been supplemented by the appearance of "A Present Day Appreciation of Beaumont's Experiments on Alexis St. Martin" by Professor Ivy of Northwestern University Medical School. In this interesting foreword Dr. Ivy presents Beaumont's experiments and conclusions in the light of modern knowledge of gastric physiology and pathology. Beaumont was signally honored by the International Congress of Physiologists in 1929. The first five chapters of the book narrate Dr. Beaumont's genealogy, and the story of his early life, his education, and his entrance into the army medical service.

The accident to Alexis St. Martin happened in the village of Mackinac, June 6, 1822, and Beaumont was his attending surgeon. From this point on the intimate details of Beaumont's investigations and experiments are spread out in the text. One wonders at the man's pertinacity and perseverance in struggling with so difficult and unstable a subject. Running through the story of these years, Myer has brought out Beaumont's relationship to army politics, his personal correspondence with physiologists and other physicians of the United States and abroad, his conclusions dealing with the various experiments, and the desertion of Alexis. Beaumont's difficulties with the publication of his experiments on gastric juice and physiology of digestion are described. Beaumont's resignation from the army and retirement to private practice in St. Louis, the running story of the changes in his life and attempts on his part to regain his subject are interestingly told.

The publishers have added an appendix regarding the later years of Alexis St. Martin who died June 24, 1880, in his late eighties, and of the successful efforts of his family to prevent a post-mortem examination. Four previously

<sup>23</sup>*Population, Race and Eugenics.* By Morris Siegel, M.D. 206 pages. Published by the author, 546 Barton St., East Hamilton, Ontario, 1939.

<sup>24</sup>*Life and Letters of Dr. William Beaumont.* By Jesse S. Myer, M.D., Late Associate in Medicine in Washington University, St. Louis. With an introduction by Sir William Osler. The C. V. Mosby Company, St. Louis, 1939.

## BOOK REVIEWS

This is a timely volume, dealing with an epoch-making type of therapy and should be of special value to all concerned in the practice of obstetrics and gynecology.

—Philip F. Williams.

The second edition of *The Diseases of the Genital Organs of Domestic Animals*<sup>21</sup> by W. L. Williams appears eighteen years after the first. It has been entirely recast and likewise shortened in text and number of illustrations. The author states that formerly great animal plagues occupied the attention of the veterinary profession, plagues such as rinderpest, foot-and-mouth disease, contagious pleuropneumonia, and anthrax of cattle. These are being brought under control, but now grave threats to physiologic reproduction are appearing. Among these the *Bacillus abortus* is one of the gravest. While tuberculosis has been reduced by one-half, abortion disease has doubled.

The medical man, particularly the gynecologist and obstetrician, will find this volume fascinating, because reproduction is controllable and supervised in domestic animals and the effect of cross and inbreeding is therefore analyzable. In other words, developmental defects can be traced as the result of determinable factors, conditions analogous to those found in the human being but unanalyzable in the human race. It is to be hoped that veterinarians will try some of the newer chemicals, such as sulfanilamide and sulfapyridine in the treatment of abortal infection, which has played such tremendous havoc in the herds of the United States.

—R. T. Frank.

Henry Pratt Fairchild, in his book, *People. The Quantity and Quality of Population*,<sup>22</sup> has put into most readable form, information usually accessible only to specialists along certain lines. The subject is of vital importance for all thinking individuals. In 1800, the population of the world consisted of nine hundred million, in 1933 of two thousand million; yet the United States and Western Europe are barely holding their own in population. Theoretically the ultimate potential capacity to increase, and this includes both plant and animal life, is governed by the egg-producing capacity of the females. "... every species in Nature, plant or animal, high or low, is equipped with a capacity to multiply sufficient to enable it to overcrowd the earth in a very short time if there were nothing to stop it." On the other hand, in this finite globe, standing room is essential and food is strictly limited. There is also a Law of Stationary Population. "Every old species in Nature increases in number up to the supporting power of its habitat, in consideration of other species struggling for existence in the same habitat." Nature consequently has had to strike a balance. In nature, except in the higher types, the infant mortality falls just short of totality by a mere fraction of a single percentage. Even among the human beings, if every couple produced fifteen children, all of whom lived and became parents in turn, the increase would be at the rate of doubling the entire human population in about every ten years.

He takes up such interesting anthropologic questions as the dispersion of man from the central Asiatic plateau. "The equipment of the human species for numerical increase, as regards biologic capacity, innate urge, and the requirements of food and standing room, is in all significant particulars similar to that of the lower organisms."

The author's conclusion appears to be that birth rate is becoming volitional instead of biologic. This is a worthwhile contribution written so as to appeal both to the professions and to the laity.

—R. T. Frank.

<sup>21</sup>*The Diseases of the Genital Organs of Domestic Animals.* By W. L. Williams, Professor Emeritus, Cornell University. Second Edition. 196 illustrations, 617 pages. W. L. Williams, Ithaca, N. Y., 1939.

<sup>22</sup>*People. The Quantity and Quality of Population.* By Henry Pratt Fairchild. Illustrated with photographs and graphic diagrams. 315 pages. Henry Holt and Co., New York, 1939.

Under ordinary circumstances the obstetrician might be considered to have little use for a text on psychiatry or psychology. On the other hand as Dr. Ebaugh states in his preface to *A Handbook of Elementary Psychobiology and Psychiatry*,<sup>28</sup> psychiatry is to be accepted more and more as a basic factor in the practice of medicine. As one reviews the psychologic reactions connected with the pregnant state and reviews the minor psychiatric reactions of many of his patients characterized by anxiety states, disorders of anticipation or even minor neuroses, one appreciates to what extent working knowledge of this subject is essential in the practice of obstetrics; while to those engaged in gynecology, the constitutional and psychic reactions of the menopause are often difficult problems.

This small handbook concisely discusses these and other problems which may face the physician in obstetric or gynecologic practice.

—Philip F. Williams.

This monograph, *Die Allgemeinbetäubung Nach Ihrem Heutigen Stand*,<sup>29</sup> by Goldhahn, is one of a series of twenty-one pamphlets on the practical aspects of surgery and edited by Von Seemen.

This is an excellent discussion of the various methods of producing general anesthesia. The author takes up the administration, physiology, and course of anesthesia. He then describes the changes which occur in the respiratory and circulatory systems and the effects upon the general metabolism, liver, kidney, circulatory and respiratory systems; with such treatment as may be necessitated, if the effects of the anesthetic agents rise to dangerous degrees.

In the second part of the monograph are discussions of the individual agents used in inhalation anesthesia, gas anesthesia, and sleep-producing drugs used either rectally or by intravenous route. Following this he discusses the various combinations which may be used, and the selection of anesthesia in systemic diseases. He presents statistics relating to the various agents, and also discusses the organization of an anesthesia department and the necessary apparatus.

There is a short discussion of anesthesia under actual conflict conditions in the war areas.

—Philip F. Williams.

In this volume, *Syphilis and Its Accomplices in Mischief*,<sup>30</sup> Dr. Katsainos discusses his ideas regarding the incurability of syphilis. In the preface of the book, which, by the way, is privately printed at Athens, Greece, the author devotes some eight pages to a beautifully written philosophic concept of man's various infirmities, including his sexual life and its relation to the spread of syphilis. The introduction to the book discusses the history of syphilis and the part which the state, physician, and society should play in restraining the ravages of the disease. Then follows a presentation of the clinical aspects of syphilis and the various drugs used in its treatment.

Again Dr. Katsainos returns to his thesis of the incurability of syphilis in a discussion of the failures of various remedies to effect a biologic, serologic or symptomatic cure. Following this there is a long discussion of the Wassermann reaction which he describes as "simply a symptom of lues." He closes the volume with a diatribe against those publishers and libraries which refused to publish or accept this book.

—Philip F. Williams.

<sup>28</sup>*A Handbook of Elementary Psychobiology and Psychiatry*. By Edward G. Billings, M.D., Assistant Professor of Psychiatry, University of Colorado School of Medicine, etc. The Macmillan Company, New York, 1939.

<sup>29</sup>*Die Allgemeinbetäubung Nach Ihrem Heutigen Stand*. Dr. Richard Goldhahn, Chefarzt des Kreiskrankenhauses Liegnitz. With 10 illustrations and 79 pages. Verlag von Ferdinand Enke, Stuttgart, 1939.

<sup>30</sup>*Syphilis, and Its Accomplices in Mischief: Society, State and Physician*. By George M. Katsainos. Privately printed at Athens, Greece, 1939.

unprinted letters of Alexis St. Martin are included, as well as abstracts of gastric fistula cases prior to that of St. Martin. A summary of the literature consulted concludes the text.

Dr. Myer's work in presenting this tribute of enduring value to Dr. Beaumont is almost as much a model of patient, persevering research as was that of the subject of his story.

—Philip F. Williams.

*What It Means to Be a Doctor*<sup>25</sup> is an intriguing little book which portrays, through the life of a fictitious Dr. James, why some 500 physicians chose the profession of medicine, at what age they determined to practice medicine, their reactions as to quality of mind and other requisites for the profession, whether or not they would want the profession carried on by their sons. The account of this self-analysis which was freely given by those who received the questionnaire makes an extremely interesting chapter on the "Psychology of the Physician." Through the life of Dr. James, the author discusses many of the problems of education and practice which confront the medical student, younger physician, and the older man of the profession today. He relates the problems of internship and preparation for specialization. He discusses very sensibly the shadow of state medicine, what the future holds for the men who are in medicine, what it holds for those in medical schools today, and a philosophic discussion on medicine closes the book.

—Philip F. Williams.

The bulk of the material presented in this manual, *Cancer Handbook*,<sup>26</sup> was assembled for postgraduate instruction at the Stanford University School of Medicine, and was originally published as a syllabus on the diagnosis and treatment of malignant tumors. That form has been preserved in order to present briefly the essential data for clinical management of cancer patients. Following a chapter on the general principles of cancer problems, the book proceeds through the elements of radiation therapy to regional carcinoma, it is profusely illustrated, and the text succinctly correlates the lesions illustrated. Rarer types of malignancy have been omitted. Of particular interest to the readers of this JOURNAL, will be the chapter on gynecologic cancer, some fourteen pages, which briefly reviews the clinical aspects and treatment of pelvic malignancy.

An excellent bibliography ends the book which should certainly be of unusual value to the average practicing physician.

—Philip F. Williams.

Vertesi has become interested in the relationship between personal and physical characteristics, as expressed in handwriting, and malignancy. In this book, *Handschrift und Eigenart der Krebsgefährdeten*,<sup>27</sup> he describes his theory that a cancerous predisposition may exist for years before the actual malignant condition has advanced to produce the usual subjective and objective phenomena, and that this predisposition may be recognized by the character of the handwriting.

He has collected a large number of specimens written before and after the advent of various malignant lesions, and uses them as illustrations of his theory. He asks that similar material for study from other countries be sent to him at Budapest.

—Philip F. Williams.

<sup>25</sup>*What It Means to Be a Doctor*. By Dwight Anderson. Public Relations Bureau, Medical Society of the State of New York. New York, 1939.

<sup>26</sup>*Cancer Handbook of the Tumor Clinic*, Stanford University School of Medicine. Edited by Eric Liljencrantz, Chief of Tumor Clinic, etc. 50 illustrations, 114 pages. Stanford University Press, California, 1939.

<sup>27</sup>*Handschrift und Eigenart der Krebsgefährdeten*. Ein Beitrag zur Dispositionsforschung. Illustrated, 297 pages. T. H. McKenna Inc., 878 Lexington Tisza, Budapest, Hungary. Y.

**Moricard, R.:** *The Artificial Development of the Human Genital Apparatus. Dosage of Oestradiol Benzoate, Testosterone Esters and the Gonadotrophins, Ann. d'endocrinol. 1: 107, 1939.*

The author feels that a more common standard of dosage of the hormones should be developed. We speak of milligrams of adrenalin and thyroxin, but one milligram of estradiol is equivalent to 10,000 mouse units, whereas 1 mg. of progesterone is termed one progesterone physiologic unit. This makes for confusion. We might better accept 1 mg. as dosage unit for sexual hormonal therapy.

In order to obtain an artificial menstruation in ovariectomized women 20 to 30 mg. of estradiol are sufficient. To induce development of the penis in a patient with the adiposogenital syndrome, it is necessary to use 100 to 200 mg. of the testosterone ester. One can produce follicular development in the human ovary by using several milligrams of the gonadotrophic serum.

The author has induced a follicular development by means of gonadotrophic hormone in ovarian vulvar grafts. This is well illustrated in two photographs.

CLAIR E. FOLSOME.

**Cordier, Devos, and Gineste:** *The Endocrine Activity of the Ovary Before Puberty, Compt. rend. de 8me Congrès. franç. de gynéc. 30: 59, 1939.*

The existence of an internal secretion of the ovary before puberty is proved by four facts: (1) Before puberty, there may be found the gonadotropic hormone A and estrin; (2) the secondary sex characters which undoubtedly depend upon the secretion of estrin are clearly perceptible from the beginning of extrauterine life; (3) recent experimental embryologic studies have demonstrated that not only the secondary sex characteristics but also the sex of the gonads depend on the secretion of the gonads, either testosterone or estrin as the case may be. Since the sex of the individual is determined early in life, a secretion must be present at this time; (4) histologic examination of immature ovaries shows that there are numerous elements which are capable of exercising an endocrine function.

It appears, therefore, that the immature ovary exercises an endocrine function but of the two hormones which are secreted after puberty only one, estrin, is secreted before puberty.

Estrin before puberty not only determines the sex of the individual and is responsible for the development of the secondary sex characters but also has an inhibitory effect on other glands of internal secretion, particularly the anterior pituitary, the thyroid, the thymus, and the adrenals.

J. P. GREENHILL.

**Hirtz, G.:** *The Uterus From the Endocrine Point of View, Rev. franç. de gynéc. et d'obst. 33: 860, 1938.*

In the experiments performed by Hirtz on rabbits, hysterectomy prevented the development of corpora lutea. On the other hand, if repeated injections of uterine extracts were given after hysterectomy, corpora lutea did appear. Hence, in the rabbit the uterus is necessary for the development of corpora lutea.

Furthermore, experiments showed that hysterectomy in rabbits does not influence the general condition of the animals, their thyroids, suprarenals, or mammary glands.

The extracts of uterus used by the author were prepared from both the myometrium and the endometrium of nonpregnant cows. These extracts failed to reveal the presence of estrin or gonadotropic hormone, hence the effect they produce on the corpora lutea is a property of their own tissue.

Clinically there is ample evidence that the uterus has an internal secretion, hence the author favors conservation of the uterus and the ovaries whenever possible. If the uterus or the ovaries must be removed, the organ which is excised must be replaced by grafts or extracts. If both uterus and ovaries are taken out, grafts of both the uterus or ovaries must be made or extracts of both organs administered.

J. P. GREENHILL.

# Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

## Selected Abstracts

### Endocrinology

May, Etienne, and Mozziconacci, P.: Moon Faces, *Ann. d'endocrinol.* 1: 28, 1939.

There is a "moon-faced" group of women who are morphologically peculiar in certain congenital characteristics which persist during those individuals' development. This group often exhibit diverse anomalies of body morphology, of metabolism, of the endocrine apparatus and neurovegetative system, and even of psyche.

Individuals of this group are short. There is a more or less accentuated obesity, usually exceeding 75 kg., which is segmentary in distribution, being localized to thighs, hips, buttocks, shoulders, and upper arms. The feet and hands are of normal or small dimensions.

This group of women present sufficient functional disorders to warrant placing them in a pathologic category. The menstrual periods are more or less abnormal, usually scanty or oligomenorrheic. Their menarche is late. The premenstrual periods are attended with dysmenorrhea. Vasomotor disturbances are frequent and are characterized by coldness of extremities, lividness of lower limbs, ocher pigmentation and a supramalleolar cyanosis. There may be an acrocyanosis of the hands and frequently there is an infiltrated red plaque with a certain degree of hairy keratosis on the posterior surface of the arms.

These patients have an excessive vascular fragility and are disposed to edema, fatigue, or even an orthostatic purpura, although the blood findings are normal. These circulatory disorders are not congenital but develop in the prepubertal period.

The secondary sexual characteristics are nearly always normal although the breasts in most cases show excessive development. The eyebrows are generally heavy. The hair is finer and more oily. Occasionally one sees a discrete upper lip hirsutism.

The group evidences a general hypotonia, the face animates slowly; the muscles are small with mediocre strength and fatigue quickly. There is a laxity of the ligaments. The blood pressure is normal and this group is not particularly disposed to hypertension. The basal metabolic rate is variable although, in general, it swings close to the normal. The lower jaw is practically always of the receding type. The blood chemistry is normal except for elevation of the serum globulin ratio.

These patients are vivacious and active in spite of their obesity. They tolerate thyroid medication poorly. Under their placid exteriors exists a force of hyperexcitability. They are sensitive, imaginative dreamers, keeping much to themselves, exhibiting an "infant" side in their characters. They find it difficult to adapt themselves to reality. Because of their body characteristics they do not appeal to men, hence show a certain unsociability with an introspective inferiority complex.

The authors conclude that this "moon-face" group of women apparently are products of a glandular and neurovegetative dystrophy. The glandular maladjustment appears to be of an hypophyseal nature, whereas the vagosympathetic factor is difficult to classify. It may have an autonomous existence or it may depend equally upon an injured hypophysis. The authors discuss possible intrauterine endocrine influences during pregnancy but conclude that most of these cases first evidence these changes rather in the prepuberty or puberty stages.

CLAIR E. FOLSOME.

When one-half of each ovary was resected, no pregnancies occurred. Corpora lutea were present in smaller numbers than usual and in some cases one remnant was resorbed, in others, atretic follicle-like change occurred throughout the ovary. Further work is to be done in this group.

The obvious conclusion is that in the rabbit, when one tube is removed, ovarian function in terms of reproduction is improved by removal of the associated ovary. Clauberg has not controlled the factor of duration of this double function by one ovary, nor is ovarian function considered in its other effects.

Schmid-Burgk has attempted to study the effects of unilateral oophorectomy in terms of the manifestations of ovarian function other than reproduction. Part of this work has already been published by Caffier (1937). The questionnaire method was used. From 519 women who had had unilateral oophorectomy, 174 usable answers were obtained. Of them 70 per cent showed some menstrual irregularity after operation. A large number of patients (61) complained of vague post-operative complaints (headache, backache, abdominal pain, vomiting, etc.). These made up a large part of the group which also reported menstrual disturbances and vice versa.

Twenty-two patients complained of postoperative subjective disturbances of the breasts, 23 of excessive weight increase, and 10 patients complained of symptoms resembling those of the menopause. Some evidence is presented to suggest that many of the patients underwent menopause but the average age for German women is the only standard used for comparison. The author concludes that unilateral oophorectomy seriously decreases the nonreproductive efficiency of the ovarian function in the human being.

(This latter article is not convincing because of the complete lack of control. Only one-third of the total operated patients is available for study. The questionnaire method is open to serious error.

The use of subjective criteria alone may be criticized. No consideration is given to the disease process requiring oophorectomy. The expected incidence of the complaints used in the nonoperated group of this particular clientele would be valuable for comparison. Reviewer.)

J. L. MCKELVEY.

**Binder, A.:** Experimental Studies of the Effect of the Follicle Hormone on the Uterine Tube, *Arch. f. Gynäk.* 168: 545, 1939.

The cyclic changes of the tubal mucosa are described and shown to be the result of direct stimulation by the follicle hormone and the corpus luteum hormone. Animal experiments are cited to prove that estrin caused increased tubal contractions in direct proportion to dosage used. Tubal contractions should therefore be most marked at the height of estrin stimulation. Such a mechanism insures maximal motility for the mature ovum and increases the opportunity of the latter to be transported to the uterine cavity after fertilization takes place.

RALPH A. REIS.

**Cramer, W., and Horning, E. S.:** Hormonal Relation Between the Ovary and the Adrenal Gland, *Lancet* 1: 192, 1939.

From experiments on mice, the authors come to the conclusion that the effects of the estrogenic ovarian hormone and adrenalectomy are opposed. They believe that the hormonal functions of the adrenal gland act synergically with the estrogenic hormone. As a result, the effects of the estrogenic hormone are diminished or arrested when the adrenals are absent. Adrenalectomy is followed by changes in the thymus, the pituitary, and the mamma which are the reverse of those produced by estrinization. Preliminary estrinization of the mouse increases its chance of surviving adrenalectomy.

In the absence of accessory adrenal cortical tissue, adrenalectomy diminishes or prevents the arrest of growth and loss of weight, the atrophy of the thymus and

Krane: **Hormone Metabolism After Removal of the Uterus**, *Zentralbl. f. Gynäk.* 63: 457, 1939.

Krane devised a method of measuring estrin quantitatively. He found that after removal of the uterus during the reproductive years there was no increase in the output of prolan, which is a sign of deterioration of the ovaries. On the other hand, estrin secretion continues for many years afterwards. The author found estrin even six years after hysterectomy, and there were cyclic variations in the amounts of estrin present. Hence, the ovaries retain their function after extirpation of the uterus.

J. P. GREENHILL.

Baidin, Alexander: **Ovarian Function Following Hysterectomy**, *Arch. f. Gynäk.* 168: 191, 1939.

The author removed the uterus in a series of experimental animals; i.e., white mice, white rats, rabbits, cats, and dogs. He examined the ovaries ten months to eight years following such uterine extirpation. He found that there was a definite decrease in the number of active and functioning follicles in the ovaries within one year following hysterectomy. In spite of this decrease and in spite of some minor anatomic changes which were found in such ovaries, it could be clearly demonstrated that the ovaries continued to function within normal range. Estrin production does not stop following extirpation of the uterus but continues for many years. The author in his conclusion therefore agrees with Sellheim in his statement that "incident to a hysterectomy the ovaries must be preserved and left in situ whenever possible."

RALPH A. REIS.

Clauberg, C.: **When Is One Ovary Better Than Two?** *Zentralbl. f. Gynäk.* 62: 969, 1938.

Schmid-Burgk, L.: **Unilateral Ovariectomy and the Climacterium**, *Zentralbl. f. Gynäk.* 62: 982, 1938.

These two reports appear together and, since they deal with a similar problem, may be reviewed together. Under the peculiar title, Clauberg reports experiments aimed at determining the value of an ovary without its tube in terms of the function of reproduction. Schmid-Burgk follows with a study of the effects of unilateral ovariectomy in the human being in terms of the postoperative adequacy of function and of the persistence of this function.

Using mature rabbits in unusually small numbers, Clauberg removed one tube, the tube on one side and the ovary on the other, tube and ovary on the same side and finally, resected portions of both ovaries. After four weeks for recovery, the animals were placed with males and, two weeks later, again operated upon.

Where one tube was removed, corpora lutea were found in both ovaries. No pregnancies were found in the horn without a tube. In the intact horn the number of pregnancies normally found in the species in one horn, or half of the normal litter were present. The ovary left on the operated side, then, was of no value in reproduction.

Where an ovary on one and a tube on the other side had been removed, excessive numbers of corpora lutea were found in the enlarged ovary. In two of the animals no pregnancies were present and in the third, seven fetuses were found in the horn with the intact tube. External migration is most unusual in the rabbit. Under any circumstances, the one ovary here may be said to have had a very questionable reproductive value.

Where an ovary or an ovary and a tube on one side were removed, interesting results were obtained. The remaining ovary enlarged and showed excessive numbers of corpora lutea. No pregnancies occurred in either group on the side where the ovary was removed. On the intact side the number of pregnancies approximated that of the total on two sides, characteristic of the intact animal of this species. The remaining ovary had taken on the reproductive function of both.



**Vignes, H.:** Ovarian Rheumatism, *Rev. franç. d. gynéc. et d'obst.* 34: 401, 1939.

In the opinion of Vignes, ovarian rheumatism is a distinct entity which occurs chiefly at the menopause but may also appear in women who are menstruating regularly, but who have ovarian disturbances. The rheumatism manifests itself principally in the knees and fingers and the lesions are frequently symmetrical. The onset of this form of rheumatism is insidious and in the advanced stages deformities set in. In many cases, the women are obese, and in some there is a congenital articular laxity which predisposes to subluxations. Many women have varicose veins. A large proportion of them have vasomotor disturbances and also hypertension without renal disease. Frequently thyroid deficiency with a low basal metabolic rate is present. On x-ray examination there is found evidence of local decalcification, osteolysis and rearrangement of calcium mobilization.

The treatment of ovarian rheumatism consists chiefly of the administration of ovarian preparations. This must begin early in the disease and continue for a long time. In addition to this therapy the patient should be given calcium, vitamin D, and phosphate preparations. In many cases orthopedic treatment must be carried out and in others, weight must be reduced.

J. P. GREENHILL.

**Shute, Evan:** Vaginitis and Vulvitis Associated With an Excess of Estrogen in the Blood, *J. A. M. A.* 110: 889, 1938.

Four cases are described showing a high content of estrogenic substance in the blood many years after the onset of the menopause. They were treated with large doses of bulk, cold-pressed, wheat germ oil, starting with 12 drachms on the first day, followed by 1 drachm or more each day. The response was good. Estrogen preparations appeared to aggravate the condition.

GROVER LIESE.

**Nelson, Warren O.:** Atypical Uterine Growths Produced by Prolonged Administration of Estrogenic Hormones, *Endocrinology* 24: 50, 1939.

The administration of estrogenic hormone preparations to 88 normal or spayed female guinea pigs has resulted in the regular occurrence of cystic glandular hyperplasia of the uterine cornua. In animals treated for several months, this condition is extended to the fundus. Such animals also show a marked adenomatous hyperplasia of the fundic endometrium. At the bases and tips of the hyperplastic glands, the epithelial cells become metaplastic. This condition of metaplasia is most marked in the cervical region where downgrowths from the epithelium penetrate the submucosa and show pronounced keratinization and pearl formation.

The uteri of 15 animals have shown multiple subperitoneal fibromyomatous growths. All animals bearing these tumors have shown periods of spontaneous vaginal bleeding. These periods have been induced in 5 animals by the withdrawal of treatment.

J. THORNWELL WITHERSPOON.

**Lipschutz, A., and Vargas, L.:** Experimental Tumorigenesis With Subcutaneous Tablets of Estradiol, *Lancet* 1: 1313, 1939.

The authors report a series of experiments with guinea pigs in which uterine and extrauterine tumors were produced by administration of estrogenic substances. Fibromas, myomas, and fibromyomas can be produced in nearly 100 per cent of the test animals. The uterine tumors are usually subserous but may be intramural and are rarely submucous. The extrauterine tumors are found most frequently in the mesometrium and mesosalpinx but may be on the abdominal wall, liver, spleen, or other abdominal organs. In earlier attempts these tumors were produced in castrated guinea pigs following the injection of estradiol, estrone, various esters, and stilbestrol. For example, 80 mg. of estradiol benzoate

the testis, the changes in the anterior lobe of the pituitary, and the hyperplasia and secretory activity of the mamma produced by estrinization. The result is the same as that produced by a continuous supply of thyrotropic hormone of the anterior lobe of the pituitary.

In 3 of 5 adrenalectomized male mice of a strain which regularly develops mammary carcinoma after estrinization, carcinoma did not develop. In the other two its development was delayed.

CARL P. HUBER.

**Shapiro, B. G.:** Control of Urinary Secretion by the Anterior Pituitary, *Lancet* 2: 1457, 1938.

Investigation of the part played by the anterior pituitary in the control of urinary secretion was carried out by the administration of estrin in order to depress the pituitary activity and by the administration of anterior lobe extracts.

Doses of 10 mg. of estradiol benzoate given to 16 patients for five or more days resulted in a significant decrease in urine output in 12. Subsequently an increased output was recorded which was greater than could be accounted for due to stored fluid. In 2 patients with diabetes insipidus a decrease in output was produced.

Pregnancy urine extracts had no effect on the urine output. Antuitrin and antuitrin-G (Parke, Davis & Co.) both resulted in varying degrees of increased output, reaching as high as 280 per cent of the preinjection level on one occasion.

The author suggests that the polyuria of Cushing's syndrome may be a manifestation of anterior pituitary hyperactivity. He feels that experimentally he has corroborated the pathologic findings of von Hann that the presence of functioning anterior lobe tissue is necessary for the production of diabetes insipidus.

CARL P. HUBER.

**Effkemann and Mueller-Jaeger:** Anterior Pituitary Lobe Insufficiency Following Severe Post Partum Hemorrhage, *Arch. f. Gynäk.* 168: 867, 1939.

The author followed up 86 women who had suffered severe post-partum hemorrhage seven to ten years previously. This was done to determine the accuracy of recent reports which claim that such post-partum hemorrhage leads to anterior pituitary ischemia and necrosis, resulting in slowly developing endocrinopathies. The group studied showed a high incidence of subsequent genital atrophy with hypomenorrhea, sterility, and adiposity. Such findings can be linked definitely to the post-partum hemorrhage. These women also showed deficiency of lactation and anomalies of menstruation. The authors believe that such findings prove that post-partum hemorrhage is frequent in endocrinopathies rather than that endocrinopathies result from post-partum hemorrhage. In other words, pathology of the pituitary gland predisposes to post-partum hemorrhage.

RALPH A. REIS.

**Gumbrecht, Keller and Loeser:** The Effect of Roentgen Irradiation on the Anterior Lobe of the Pituitary Gland, *Klin. Wchnschr.* 17: 801, 1938.

The authors investigated the effect of roentgen irradiation on the anterior lobe of the pituitary gland of various laboratory animals, such as white mice, rats, and rabbits. They were unable to produce any type of structural change even when the animals were subjected to intensive irradiation. Unilateral irradiation of the hypophysis produced no changes in the quantity of thyrotropic or gonadotropic hormone. When both normal and castrated animals were subjected to repeated irradiation of the entire skull, a fatal cachexia was produced in each instance. This was probably due to a failure to secrete both the thyrotropic and gonadotropic hormones although no structural changes could be found.

RALPH A. REIS.

amount of bleeding decreased but the menses were not regular. In these cases there was a long period of amenorrhea before the menses reappeared. In two cases the menorrhagia persisted in spite of the treatment with estrin.

In three of the juvenile cases, curettement revealed glandular hyperplasia. This condition the author believes is due to persistent action of the corpus luteum hormone and not to an insufficiency of this hormone as is generally believed. Hence, he maintains this condition should be treated with estrin and not with progestin.

The author also used estrin with or without corpus luteum in 5 patients with secondary amenorrhea and oligomenorrhea and observed cures in 3 patients and improvement in the other 2 patients. Bleeding occurred in patients during or immediately after the treatment ceased.

J. P. GREENHILL.

Saulnier, F.: *Therapeutic Use of Progesterone and Its Cytologic Effect on the Uterine Mucosa*, Bull. Soc. d'obst. et de gynéc. 28: 148, 1939.

After the administration of 10 to 20 mg. of testosterone, the author failed to observe the appearance of glycogen in the uterine mucosa of oophorectomized women. In three women with functional menorrhagia, progesterone brought about a cessation of the bleeding. In two cases of amenorrhea, this hormone produced a reappearance of normal menses, contrary to the common belief concerning the effect of progesterone. In two cases of repeated spontaneous abortion, the corpus luteum hormone prevented interruption of the gestation. In some cases the dose used was very high, as for example in one case of threatened abortion in which 92 mg. was used.

J. P. GREENHILL.

Zondek, B., and Rozin, S.: *Uterine Hemorrhage Induced by Oral Administration of Pregneninonol*, Lancet 1: 504, 1939.

Zondek and Rozin have previously reported the effectiveness of progesterone in initiating uterine hemorrhage during the intermenstrual stage in normally menstruating women by intramuscular injection of 10 mg. of progesterone daily for five days, beginning shortly after menstruation. They have also reported its effectiveness in secondary amenorrhea without preliminary estrogenic therapy. Progesterone therapy is a failure in primary amenorrhea. It is not effective by mouth. The authors report similar results in a normally menstruating woman and in a patient with secondary amenorrhea, following the oral use of pregneninonol in a total dose of 300 mg. given in 5 daily doses. This synthetic substance is then apparently active by mouth in dosages approximately 6 times greater than the effective dose of progesterone intramuscularly. The effective dosage of estrogenic hormone by mouth is 5 times greater than that by parenteral administration.

CARL P. HUBER.

Fluhmann, C. H.: *Endocrine Theories of Dysmenorrhea*, Endocrinology 23: 393, 1938.

A series of 85 tests for estrogenic substances in the blood was conducted on 19 patients with primary dysmenorrhea. In 18 instances the results failed to show any variation from the normal. There are serious objections to accepting any of the theories which seek to explain the cause of primary dysmenorrhea solely as a deficiency or excess of either estrogen or progestin.

J. THORNWELL WITHERSPOON.

Murless, B. C.: *Effect of Follicular Hormone on Menopausal Flushes*, Lancet 1: 1205, 1939.

A series of 51 patients with menopausal flushes, developing following radiation, were treated with small doses of estradiol by mouth. Therapy was begun eight

injected subcutaneously three times weekly for two to three months rarely failed to produce tumors. The authors now show that by introducing tablets of estradiol under the skin to insure continuous absorption of the hormone, tumors may be produced in as short a period as 2.5 to 3 weeks and are almost constantly produced by seven weeks. They used 20 and 50 mg. tablets and with both sizes an average of 4 mg. was absorbed per month. The tumors in all instances regressed following discontinuation of therapy, so that the authors suggest the term "tumorigenic" to describe the effect of the estrogenic substance. No malignant tumors were produced.

CARL P. HUBER.

Lipshutz, A., Murillo, R., and Vargas, L.: Antitumorigenic Action of Progesterone, *Lancet* 2: 420, 1939.

These workers have previously reported the production of fibromyomas, both uterine and abdominal, in the experimental animal with various estrogenic substances. They now report the inhibition of the phenomenon by the coincident injection of progesterone.

Five castrated guinea pigs were treated three times weekly with 80 mg. estradiol given subcutaneously in oil. Two were treated for forty-seven days and three for ninety days. All revealed uterine or extrauterine tumors at autopsy. A second group of five guinea pigs received the same treatment with estrogenic substance, but after the first thirty days were given 12 mg. of progesterone in oil three times weekly. Only one of this group developed a tumor.

While recognizing that this is a small series, the authors feel that it strongly suggests an antitumorigenic action of progesterone. The quantity of progesterone necessary to suppress completely the effect of the estrogenic substance is more than 150 times greater than the latter. They feel that their results support the hypothesis that the development of uterine fibromyomas in women is due to an imbalance between follicular and luteal hormones and that progesterone may prove useful as a therapeutic agent against fibromyomas.

CARL P. HUBER.

Hain, A. M., and Robertson, Edwin M.: Pregnandiol Excretion in the Menstrual Cycle, *Brit. M. J.* 1: 1226, 1939.

The authors make use of the fact, that the excretion of pregnandiol is directly related to corpus luteum hormone secretion in the body in a study of five patients suffering from sterility. In addition to the pregnandiol determinations, histologic examination of endometrial scrapings was made, the two being done independently and without knowledge of the findings obtained or information as to the stage of the cycle. All but one of the patients was followed through 2 menstrual cycles. At only one time in one case was there any divergence between the histologic and excretion findings, a definite correlation being present elsewhere. No pregnandiol was excreted during the early or the proliferative phase of the cycle, and pregnandiol excretion was found in all patients having a secretory endometrium. On the basis of the normal figures for pregnandiol excretion as determined by Venning and Brown, the authors attempted to estimate the normality of ovarian function. The correlation of the histologic and excretory findings is further confirmatory evidence that there is a direct relationship between pregnandiol excretion and corpus luteum hormone secretion in the body.

FRED L. ADAIR AND JOHN NEWDORP.

Anker, H.: Menstrual Disturbances Treated With Estrin, *Acta obst. et gynec. Scandinav.* 19: 9, 1939.

The author employed large amounts of estrin in seven cases of menorrhagia including six of the juvenile type. In two cases following this therapy, the menses were normal in amount and frequency. In three additional cases, the

## Item

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### American Board of Obstetrics and Gynecology

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted at Atlantic City, N. J., from Friday, June 7, through Monday, June 10, 1940, prior to the opening of the annual meeting of the American Medical Association in New York City on Wednesday, June 12, 1940. Formal notice of the exact time and place of the examination will be forwarded to each candidate several weeks in advance of the examination dates. Group A candidates will be examined on June 7 and 8, and Group B candidates on June 9 and 10.

Candidates for *reevaluation* in Part II must make written application to the Secretary's Office *before April 15*.

The annual dinner of the Board will be held in New York City on Wednesday evening, June 12, 1940, at the Hotel McAlpin. Diplomates certified at the preceding days' examinations will be introduced personally, and there will be several speakers. All Diplomates of the Board, and others interested in the work of the Board, are cordially invited to attend this dinner. Tickets at \$3.50 each may be obtained from Dr. Joseph L. Baer, chairman, 104 S. Michigan Avenue, Chicago, Illinois, or at the registration desk during the examinations.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

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## Books Received

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SEXUAL PATHOLOGY. By Magnus Hirschfeld, M.D. Authorized Translation by Jerome Gibbs. Originally published in three volumes. 368 pages. Emerson Books, Inc. New York, 1940.

COMBINED TEXTBOOK OF OBSTETRICS AND GYNECOLOGY. Revised and re-written by J. M. Munro Kerr, R. W. Johnstone, James Hendry, Dugald Baird, James Young, Donald McIntyre, E. Chalmers Fahmy, with additional contributions by Charles McNeil and G. Jackson Wilson. Third edition, 1,192 pages with 499 illustrations and numerous x-ray plates. Williams and Wilkins Company, Baltimore, 1939.

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## Erratum

### *Pituitrin in Hemorrhage*

In the summary of the papers on Pregnancy Hemorrhage in the March, 1940, issue, page 538, paragraph 4, the sentence "These speakers seem agreed that obstetric pituitary at the end of the first stage is helpful," should read, naturally, "at the end of the second stage."

to twelve weeks after radiation. The dosages used were 0.1 mg. estradiol daily for two weeks, increased at that time if indicated to 0.15 or 0.2 mg. daily for four weeks when a gradual decrease to 0.05 mg. daily was begun. Every fifth patient was given pure lactose tablets similarly dispensed. The effect of the treatment was estimated by change in the severity and duration of flushes and by a written record of the number of flushes per twenty-four hours. In none of the controls was the number of flushes decreased, although some patients reported less severe flushes. In the other group, 11 were completely cured. In only 5 patients was there no reduction in the number of flushes and in the remainder there was definite improvement. Dosages were purposely kept low in an attempt to demonstrate the effectiveness of therapy at reasonable cost and without hyperdermic treatment.

CARL P. HUBER.

Bishop, P. M. F.: A Clinical Experiment in Oestrin Therapy, *Brit. M. J.* 1: 939, 1938.

Because estrin has such a well-established place as a therapeutic agent, an experiment on a 20-year-old human female castrate was done to determine the most effective mode of administration. Results were judged on how well menopausal subjective symptoms were controlled and also on the production of "estrin threshold bleeding." This term refers to the intermittent bleeding occurring during the period of estrin administration.

Giving estrin by mouth in quite small doses was effective in controlling symptoms. The level of estrin threshold bleeding was found to be between 5,000 and 6,000 I. U. by injection and 25,000 to 30,000 I. U. by mouth. This suggested a peroral-intramuscular ratio of 5:1.

A 14 mg. tablet of crystalline estrone was implanted subcutaneously and was effective in controlling symptoms for four or five weeks.

F. L. ADAIR AND JOHN A. HAUGEN.

Sakanouje, K.: Experimental Investigation of the Percutaneous Absorption of Estrin, *Jap. J. Obst. & Gynec.* 22: 2, 1939.

The author studied the urine of three women to determine the effect of rubbing estrin into the skin. Two of the women were in the reproductive period but had a subnormal amount of estrin in the urine and one woman had passed the menopause. The urine from the latter patient had failed to reveal any estrin. In each case three analyses of the urine were made and in each instance the examinations were made over a period of three days. In two cases the author found a distinct increase in the excretion of estrin after this substance had been rubbed into the skin. Hence, he concludes that in human beings, as well as in animals, estrin is absorbed through the skin.

J. P. GREENHILL.

Eanesly and Parkes: Further Experiments on the Administration of Hormones by the Subcutaneous Implantation of Tablets, *Lancet* 2: 606, 1938.

The effectiveness of crystalline gonadal hormones when administered by subcutaneous implantation of the solid tablets of the pure substance is reported. In the rat, estradiol is absorbed nearly twice as fast as estrone, while testosterone is absorbed much faster than estrone and somewhat faster than testosterone propionate. Using tablets up to 100 mg. in size, the following rates of absorption per month are given: estrone, 2.5 to 10 per cent; testosterone propionate, 15 per cent; and testosterone, 25 per cent.

In order to increase the dosage, the size of the tablet is not increased but multiple implantation of small tablets is suggested. It is concluded that the technique is particularly useful where a long continued steady effect is required, as, in the depression of the gonad-stimulating and growth-promoting activity of the pituitary by the estrogens, and in the masculinization of the female by the androgens.

CARL P. HUBER.

Social, economic, and psychic factors are less obviously related to spontaneous abortion. Nevertheless their indirect influence must be acknowledged. Dramatic cases in which violent emotions, fear, grief, anger, are followed by the immediate onset of labor pains and vaginal bleeding, are well authenticated. These are the exception. That the mixed psychologic and sociologic factors of poverty, toil, anxiety, defective diet, and neglected health contribute to spontaneous abortion, while more difficult to prove, appear obvious. That these factors are often ineffective in interrupting pregnancy is, of course, shown by the number of children carried to term by women who are burdened by them all.

It is unnecessary to point out the major importance of the abortion problem. The estimates of its magnitude as presented conservatively by Taussig are too familiar to be repeated here. The reason that these estimates are so familiar is that Taussig's is actually the only book in the English language which even attempts a comprehensive analysis of the subject. Considering its great social significance, it is truly incredible that so little has been written about abortion. The extent of our ignorance is boundless. That is the only excuse for presenting the crude and incomplete data offered here.

In a fairly diligent search for series comparable to the present one, only 14 papers which analyze groups of cases admitted to hospital under the diagnosis of "abortion" and which offer any descriptive data on the sample of population involved have been found in the English and American medical literature of the past ten years. Even in these, the data are meager in the extreme, color, marital status, and religion being usually all that is reported.

The question of whether or not the abortion was induced assumes paramount importance in the minds of most investigators. The majority, however, note the impossibility of certainty in obtaining an answer to this question.

There is no reasonable doubt that many patients deliberately and persistently lie in denying induction. Their motives are fear of punishment or moral censure and/or loyalty to the abortionist whom they consider their helper. There is also little doubt that others who admit induction freely are the dupes of coincidence and have actually undergone a spontaneous abortion soon after taking a hot bath or a cup of ginger tea. Still others, in both groups and also in the group who convincingly claim that they have had a "miscarriage," prove actually to be suffering from various pelvic conditions unassociated in any way with pregnancy. The latter group is particularly interesting because of its vitiation of any statistical study based on the statement of the patient about her past history. In our series of 537 cases there were 67 (12.4 per cent) whose final diagnosis was "not pregnant." Twenty-two of these patients will go around for the rest of their lives glibly telling all history takers that they had an "abortion," while 45 will as freely state that they had a "miscarriage."

The difficulties in arriving at a correct appraisal of circumstances surrounding the abortion do not stop when the momentous question "in-

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## Original Communications

### SOME SOCIOLOGIC AND PSYCHOLOGIC OBSERVATIONS ON ABORTION\*

#### A STUDY OF 537 CASES

VIRGINIA CLAY HAMILTON, M.D., NEW YORK, N. Y.

*(From the Department of Obstetrics and Gynecology, New York University College of Medicine and the Obstetrical and Gynecological Service of the Third [New York University] Surgical Division, Bellevue Hospital)*

THAT induced abortion is primarily a sociologic and psychologic problem is self-evident. If conditions did not exist which make offspring undesirable, to the particular woman at the particular time, there would be no induced abortion. If every married woman felt her family budget sufficient to provide satisfactorily for unlimited children, if there were no social stigma associated with illegitimacy, the incidence of induced abortion would, no doubt, be reduced to a fraction of its present magnitude. The relative nature of economic and social pressure must be stressed. An income which would seem ample for four children to a woman accustomed to one standard of living would seem to another hopelessly inadequate for one. Illegitimacy is accepted in certain social groups with no more than a passing sneer, in others it means ruin to the mother and lifelong handicap to the child. Other, more subtle, factors play a part in the problem. These, too, vary from group to group and from woman to woman within the group. Aleck Bourne has recently presented an analysis of these factors in an address to the Edinburgh Obstetrical Society which for clarity and good sense excels any similar discussion known to the author.

\*Aided by a grant from The National Committee on Maternal Health, Inc. Read at a meeting of Round Table Discussion Group, under auspices of the National Committee on Maternal Health, Inc., January 31, 1940.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."



to tell their stories freely, but were interrupted for answers to specific questions where those did not appear spontaneously. An effort was made to refrain from leading questions. Each interview occupied from one-half to one hour and many patients were visited repeatedly on successive days. Several who denied induction at the first questioning later admitted it. Two, who were most persistent in denial, in terminal delirium described their experience with the abortionist. At the end of the interview a note of the examiner's estimate of the patient's reliability was made. True, false, or doubtful applied principally to the statement of induction, since many patients appeared perfectly candid in their answers to all other questions, deceptive on that point alone. As a whole the group showed surprisingly little reluctance to discuss the intimate questions which were put to them. A few seemed disinclined to discuss their sex life. These were not pressed to do so.

It seems hardly necessary to point out the extreme selection evidenced by the very admission of these patients to Bellevue. This fact alone places the overwhelming majority in those much discussed fractions of our total population, the "one-third of a nation" whose housing conditions are atrocious and the "submerged tenth" whose finances never were and possibly never will be consistent with even a modest standard of comfortable living. The unwisdom of applying any observation here recorded to any other population group is self-evident. Ideas of economic sufficiency are relative, however, human nature does not vary greatly and the same motives, reactions, and attitudes may be found, though doubtless in varying proportions in other groups of "higher society."

#### MATERIAL

Our group consisted of 156 patients (29 per cent) who admitted induction, 346 (64.5 per cent) who denied it, and 30 (5.5 per cent) who were referred for therapeutic abortion. Five, diagnosed "abortion" on admission, proved to have ectopic pregnancies and were included in the therapeutic group, raising it to 35. Seventy-two per cent were married women, 12 per cent single, and 16 per cent previously married (widowed, separated, or divorced). The low proportion of married women as compared to other series in this country (80 to 92.3 per cent) may be due to the high proportion of negroes in our sample (34 per cent). Of these, only 59 per cent were married and still living with their husbands. It may also be due to our classification, as in several of the other studies only two categories are considered, ever married and single. The latter classification would give us 88 per cent married women, 92 per cent white married, and 68 per cent negro married. Among the married, color plays no significant part in the type of abortion. Twenty-two per cent of the white married women admitted induction, 24 per cent of the negro. The difference in behavior between the white and negro single groups is significant. Sixty-four of the single white women admitted induction, while but 40 per cent of the unmarried negroes did so. Still more striking is the difference between the two previously married groups; the negroes behaving essentially like those still married (28 per cent), while the whites showed nearly twice the frequency of induction (52 per cent) (Table I).

Our patients varied in age from 13 to 49 years. Neither of the extreme cases was found to have been pregnant. Although the little girl admitted coitus and although her mother had plied her with oxytocics, the pathologic report established her diagnosis as cystic and glandular endometrial hyperplasia. The older woman, though equally chagrined by the prospect of an addition to her family, proved to be suffering from fibromyoma uteri. The youngest actual abortion case was 15,

duced" or "spontaneous" is answered. Intentional deception, unintentional misinterpretation, and candid truth-telling mingle in varying proportions in the mass response to each question. Many of the answers undoubtedly represent the patient's idea of what *ought* to be the case and are a half-conscious attempt to deceive not only the investigator, but herself as well. The overwhelming majority of married women who said they loved their husbands is an example. The few who expressed dislike went against convention and did so with an effort. Conversely it is conventional for a single girl to abhor her seducer, hence those who declare that they "still love him" do so with bravado.

The same applies to the statement of childhood experience. Those who loyally claim that they had happy homes and that their fathers provided amply for all their needs are probably far in excess of the actual number who were brought up under these idyllic circumstances. Recognizing the practical impossibility of disentangling the true from the false or equivocal and with the profound humility of an investigator who does not set up to be in any sense a sociologist or a psychologist, the author presents the following data in the hope that others who are better qualified may be inspired to dig more deeply into the mine which is here barely opened.

Although the group who admitted drug or thermal induction conform clinically much more closely to those whom we believe to have had truly spontaneous abortions, and although a subgroup of those who denied induction, that subgroup which the examiner considered untruthful, conforms in most respects to the mechanically induced group, we have thought best in this particular study to make our classification purely on the basis of the patient's statement. We are concerned here not with treatment nor prognosis, but with motivation and behavior. The woman who soaks her feet in mustard water and takes pills has the same purpose in mind as the one who visits the abortionist. Hence our cases are divided into "induced" and "spontaneous" according to the patient's admission or denial that she voluntarily did anything with the intention of interrupting the normal course of her pregnancy.

Beginning May 1, 1938 and continuing almost daily until July 15, 1939, the author interviewed all but 50 of 537 consecutive patients who were admitted to the Gynecological Ward of Bellevue Hospital for symptoms associated with an interruption of pregnancy before the twenty-eighth week. The 50 patients excepted were interviewed by Dr. Katherine Miller. Admission diagnosis included threatened, inevitable, incomplete, complete, and missed abortion and also 30 cases referred from the medical service for therapeutic abortion. An effort was made to see all patients within twenty-four hours of admission and before active treatment, as it was thought that they would talk more freely if they felt that the interview had some immediate bearing on the care they would receive. The interview was as nearly private as ward conditions would permit, and, when necessary to gain co-operation, the patients were assured that the information they gave was strictly confidential, would not be filed under their names, and would not be included in their hospital records. They were encouraged

influenced by convention. They are simply responses to the questions, "Did you have a happy childhood? Was it hard for your parents to supply you with necessities or did you have plenty? Do you still keep in touch with your family?" About two-thirds of all patients who were questioned (54 were not) answered unequivocally that their childhood had been happy and carefree, one-fifth had been frankly unhappy and suffered hardships, while the remainder reported a fairly happy childhood marred by the memory of some flaw such as poverty or unkindness on the part of father or stepmother. About half of the patients in each abortion category stated that they were in close touch with those of their families who were still alive and nearby. A fifth seldom saw their close relatives but were on good terms with them and kept up a correspondence. Eleven per cent of the spontaneous group stated that they had no close relatives living, but only 3 per cent of the induced were so bereft. On the other hand, twice as many (15 per cent) of the latter were on bad terms with their families. Only 8 per cent of the spontaneous mentioned quarrels and ill-feeling.

The sexual partners (husbands or otherwise) of about one-half (52 per cent) of these patients were employed in private enterprise. An additional 25 per cent were employed on relief projects or received regular government support of some sort. The remainder were either unemployed and not receiving relief (16 per cent) or else engaged in occupations unknown to the woman or uncommunicated to the examiner. There was no significant difference in the employment status of the male partners of the different abortion groups.

When the number of living children was correlated with the employment status of the man, the usual relationship was found: relief recipients had the largest families, unemployed nonrelief recipients next, and those employed in private enterprise the smallest. One hundred and ninety-one patients (36 per cent) had no living child; 39 per cent had 1 or 2 children and the remaining 25 per cent had 3 or more. The distribution of living children was approximately that of chance expectancy for the induced and spontaneous groups.

Thus, two important potential reasons for induction, too large a family and low economic status, did not characterize the induced abortion group in a manner significantly different from the spontaneous and therapeutic groups.

When, however, we turn from the employment of the father to that of the woman herself we find a wholly different state of affairs (Table III). Many

TABLE III. PATIENT'S STATEMENT OF TYPE OF ABORTION BY MARITAL STATUS AND BY WOMAN'S EMPLOYMENT\*  
(Selected Groups and All Cases)

	CASES	%	MARRIED	%	PREVIOUSLY MARRIED	%	SINGLE	%
Induced (mechanical)	52	100	28	100	7	100	17	100
Employed	26	50	6	21	5	71	15	88
Unemployed	2	4	--	--	--	--	2	12
Housewife	24	46	22	79	2	29	--	--
Spontaneous (true)	158	100	146	100	7	100	5	100
Employed	42	27	35	24	5	70	2	40
Unemployed	4	2	2	1	1	15	1	20
Housewife	112	71	109	75	1	15	2	40
All cases (except therapeutic)	502	100	362	100	74	100	65	100
Employed	158	31	79	22	41	55	38	46
Unemployed	36	7	7	2	17	22	12*	18
Housewife	308	62	277	76	16	23	15	46

\*Including 6 students.

more than expected of the induced group were employed while many more of the spontaneous group were housewives. If the extreme groups, those who admitted mechanical induction and those who convincingly denied all interference, are compared, we find that the proportion of the former who were employed is twice

TABLE I. PATIENT'S STATEMENT OF TYPE OF ABORTION, EXAMINER'S ESTIMATE OF VERACITY, COLOR AND MARITAL STATUS

	CASES	%	INDUCED (MECH.)	%	INDUCED (DRUG)	%	SPONT. (FALSE)	%	SPONT. (DOUBT.)	%	SPONT. (TRUE)	%	THERA.	%
White	353	100	42	12	62	18	21	6	88	25	112	32	28	7
Married	279	79	23	8	39	14	13	5	75	27	108	39	21	7
Previously married	46	13	7	15	17	37	5	11	11	24	2	4	4	9
Single	28	8	12	43	6	21	3	11	2	7	2	7	3	11
Negro	184	100	10	5	42	23	11	6	68	37	46	25	7	4
Married	108	59	5	5	21	19	4	4	36	33	38	35	4	4
Previously married	36	19	-	-	10	28	3	8	15	42	5	14	3	8
Single	40	22	5	12	11	28	4	10	17	43	3	7	-	-
Totals	537	100	52	10	104	19	32	6	156	29	158	29	35	7

the oldest 47. As in all comparable series, the great majority (73 per cent) of patients were between 20 and 35. More than half (57 per cent) were between 20 and 30. The average age for all patients was 27.8 years. For those admitting induction it was nearly a year younger, 26.9. No appreciable difference in age distribution could be demonstrated between those giving a history of interference and those who denied it.

Four hundred and twelve patients (77 per cent) were born in the United States, while 123 (23 per cent) were foreign born and the nativity of 2 was un-stated. Eighty-five per cent of those admitting induction were native born. The average education of the group was 7.5 years grade school. There were, however, significant differences in educational attainment between native born and foreign born, and between the "induced" and "spontaneous" groups. The native born were the better educated in all groups classified according to type of abortion. More of those who admitted induction, fewer of those who denied it, had attained high school than expected (Table II).

TABLE II. PATIENT'S STATEMENT OF TYPE OF ABORTION, BY EDUCATIONAL ATTAINMENT OF THE WOMAN AND BY NATIVITY

	CASES	%	COMPLETED GRADES												HIGHER	%
			0	%	1-7	%	8	%	9-11	%	12	%				
Induced	156	100	3	2	48	31	34	22	46	29	22	14	3	2		
United States	132	85	2	2	34	26	32	24	42	32	19	14	3	2		
Foreign	24	15	1	4	14	58	2	8	4	17	3	13				
Spontaneous	346	100	14	4	109	32	104	30	88	25	24	7	7	2		
United States	258	75	1		69	27	85	33	75	29	21	8	7	3		
Foreign	88	25	13	15	40	45	19	22	13	15	3	3				
Therapeutic	35	100	1	3	10	29	11	31	6	17	6	17	1	3		
United States	24	69			5	21	8	33	5	21	5	21	1	4		
Foreign	11	31	1	9	5	46	3	27	1	9	1	9				
Totals	537	100	18	3	167	31	149	28	140	26	52	10	11	2		
United States	414	77	3	1	108	26	125	30	122	29	45	11	11	3		
Foreign	123	23	15	12	59	48	24	19	18	15	7	6				

While considering nativity and education, we may as well turn to the childhood experience of these patients and to their present relations with their parents and siblings. These data, as has been said, are crude in the extreme and largely

vasion of privacy, but, as was said earlier, the answers are probably of little value. They are presented for what they may be worth. The observed data are closely in accord with chance expectancy, except for the high incidence of dislike for the partner (33 per cent), expressed by the single women in the induced group. Over 80 per cent of the married women stated that they loved their husbands. Seventy-three per cent of all patients frankly enjoyed coitus with their present partner. Eighty-seven per cent experienced orgasm with him though the majority qualified their statement by "sometimes" or "occasionally." Coital frequency varied greatly though the mode for all ages was "weekly or more but less than daily." Only 12 patients reported daily coitus. Three of these were in the 20 to 24 age group, 1 in the 25 to 29, 3 in the 30 to 34, and 1 in the 35 to 39. The other groups, "monthly but less than weekly" and "less than monthly," were similarly unaffected by age although age was shown to parallel duration of sexual experience closely.

One hundred and eighty-four of these patients (37 per cent) denied ever having heard of the existence of birth control clinics; 294 had heard of them from friends, relatives, doctors, nurses, or social agencies, but had never visited one. Only 53 (10 per cent) had been instructed in the diaphragm and jelly technique. Sixteen of the latter were using the method prior to this pregnancy, but few attributed conception to its failure. Most of the 16 confessed neglect to protect themselves on one or frequent occasions.

In contrast to the relatively small number who had availed themselves of medical counsel with regard to contraception, only 58 said that they or their husband were opposed to it on religious or other grounds, and 346 were using some method to prevent pregnancy at the time this conception was supposed to have occurred. An additional 24 had previously made contraceptive efforts but stated that they had suspended these for a planned pregnancy. One hundred and sixty-three denied any recent attempt to limit their fertility, but 20 of these acknowledged earlier contraception, leaving 143 who denied ever in their lives having used any method whatever to this end. Fifty-one of the noncontraceptors were primigravidas.

Of the contraceptive methods used by patients who had had experience with only one, douching was the most popular. Its use was reported by 90. Forty had relied on the condom and 31 on withdrawal. One hundred and forty-six, however, stated that they had used 2 or 3 of these (douche, condom, withdrawal) alternately or in combination. Only 39 reported the use of other methods (suppositories, pessaries, "the rhythm," etc.) immediately preceding this pregnancy.

All of the women were warned of the inadvisability of immediately becoming pregnant again regardless of their ultimate wish for a child. They were then questioned about their plans for avoiding this contingency. Two hundred and seventy-six (55 per cent) said they would like to be referred to Birth Control Clinics and were thereupon given definite written directions as to the address and hours of the nearest clinic to their homes. Nine were sterilized in connection with therapeutic hysterotomy. Sixty-nine (14 per cent) said they intended to abstain from coitus. Half of these were in the group who had induced abortion and most were single. One hundred and sixteen (23 per cent) intended to return to their former habit of contraception or noncontraception, and 5 per cent stated that they intended to resume their efforts to conceive immediately. Seven per cent were undecided as to their future course of action.

#### SUMMARY

The single, the white, the employed, the native American, the more highly educated woman was found significantly more frequently in the group who admitted induced abortion than among those who denied it. Women who felt a sense of economic pressure or shame, those who expressed no desire for a child, and those who had practiced contraception intensively howbeit ineffectively, were also significantly more frequent.

that of the latter, conversely 46 per cent of the former and 71 per cent of the latter were housewives. Here, too, marital status was largely responsible for the difference. Employed married women were somewhat less frequent in the induced group.

Overcrowding is often suggested as a potent cause for family limitation. Here again it must be remembered that the concept of overcrowding is relative. In our series the proportion of patients having more to those having less than two persons per room was practically the same in the induced and spontaneous groups. Thirty-six per cent of the induced group had more than 2 persons per room while this was true of 39 per cent of the spontaneous. In this study a child, even a small baby, was counted a person, hence the degree of crowding was less than would appear if "person-units" rather than persons were considered.

But persons-per-room does not tell the whole story. A married couple may share a single room and not feel particularly overcrowded, whereas 8 persons in a four-room flat may seriously interfere with each other's activities. Persons per household may be a more important factor conducive to induction. As will be shown later, the majority of patients in all categories stated that they considered two or three children an ideal number. Twenty per cent of the induced group had more than five persons in their household, while 14 per cent of the spontaneous group were overcrowded in this sense. However, this grouping is probably not valid as a significant number of patients considered 4 or 5 children desirable.

Although nearly two-thirds denied having taken any active step to rid themselves of the fetus, only a little over one-third denied that they had reasons for wishing interruption. Forty per cent declared that economic considerations made the birth of the child undesirable; 52, or one-third of those not living in wedlock, were influenced by shame. Thirty-six gave ill health as a reason, 24 of these belonging to the therapeutic group. Twenty-three had ideas of family planning and an equal number gave a variety of other causes. Only 2 of these mentioned fear of childbirth as a motive.

When asked if they would want a child, or an additional child, under more favorable conditions, the proportion just stated was reversed. A little over two-thirds (including half of those who were then hospitalized because of induced abortion) said "yes," while less than one-third said "no, they would have no such wish under any circumstances." This is at variance with the response of Pearce's English group. Only 25 per cent of these wished a child.

The average prior parity of the previously gravid group was 1.5, prior gravidity was 2.4; previous abortions, 0.8 (induced 0.3, spontaneous 0.5). One hundred and twenty-three patients had never given birth to a viable child and 191 had no living child at the time of the interview. But when asked what would be an ideal number of children under most favorable circumstances only 5 stated that an 0-child family would be desirable. The most popular size was the 2-child family which 204 patients preferred. Eighty-four per cent were in favor of 2- to 4-child families for those who were able to bear and care for them. In responding to this question which was, in effect, an invitation to build a castle in Spain, the induced and spontaneous groups showed no significant difference. The ideal families of negroes and whites were substantially the same.

The feelings expressed with regard to the current abortion were possibly largely influenced by convention. Two hundred and forty-eight patients expressed regret while 210 stated that they felt relief or satisfaction. Over half of the induced group gave voice to the latter state of mind, while 30 per cent of those who denied interference were also glad to be relieved of the prospect of a child. Twenty-three per cent of the induced said they regretted the termination of their pregnancy, as did 61 per cent of the spontaneous. Fourteen patients, 11 in the induced and 3 in the therapeutic group, expressed remorse. Twelve felt frightened by their condition.

Since unhappy marital adjustment is sometimes thought to play a part in influencing a woman to reject pregnancy, our patients were questioned with regard to their feelings about their sexual partners and coitus. These questions were answered in most cases without apparent reserve or resentment at the in-

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## WEIGHT CHANGES DURING PREGNANCY AND PUERPERIUM

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THE observation that gestation is accompanied by a progressive increase in weight of the mother, beyond that directly and indirectly attributable to the offspring, has continued to intrigue many investigators ever since Gassner first recorded this seemingly unnecessary weight gain. The association of excessive weight increase in the eclamptic syndrome, as shown by Zangemeister and several subsequent writers, adds further interest to this problem.

Of the numerous recent contributions that are of significance in connection with the findings in the present paper are those of Wodon, Evans, Siddall and Mack, McIlroy and Rodway, and Bray, to mention only some. Wodon directed attention to the importance of weight gain when expressed in terms of percentage of initial weight as contrasted with absolute weights. Bray emphasized the factors that do and those that do not influence weight gain. The English authors, as well as Siddall and Mack report the abnormal changes noted in certain of the toxemias of pregnancy.

As there appear to be marked differences in the published observations on gain and loss of weight associated with gestation and the puerperium in both normal and abnormal patients, we have deemed it advisable to correlate the weight changes during pregnancy and puerperium. It has been our routine practice, since September, 1932, to weigh all pregnant and puerperal patients at stated times, including those immediately before and after delivery.

Religious affiliation, age, prior gravidity, prior parity, previous abortions, number of living children, enjoyment of coitus, feeling for sexual partner, employment of the latter, childhood experience, emotional relation to parents and siblings, number of siblings, number of persons per room, concept of size of ideal family, although perhaps influential in individual cases, did not show statistically significant differences in the groups characterized by admission or denial of interference.

The facts cited show that legal and religious disapproval mean little to the woman who is interested in limiting the size of her family. She uses such methods to prevent pregnancy as she and her partner know, and, when these fail, in many instances she takes drastic steps to rid herself of the fetus.

The most obvious first step toward reducing the incidence of abortion would be to provide the woman, who has recently given proof of the seriousness of her desire to limit her family, with more reliable methods of contraception than those she has previously tried. There would be fewer abortions, both induced and spontaneous, if every postabortal patient were routinely advised to refrain from immediate pregnancy, instructed in the way of carrying out this advice and fitted with a pessary (provided she desired it and this method were suitable in her case) at her follow-up visit to the gynecologic clinic.

Next in preference would be an intramural birth control clinic closely cooperating with the gynecologic and obstetric clinics.

Since political and religious opposition render both of these plans unfeasible in many hospitals, the next best thing would be to offer every patient of this type a definite reference to the birth control clinic most convenient to her home.

Popularization of the Aschheim-Zondek test and provision of this service at cost would reduce the incidence of "abortion" in the non-pregnant.

Although greater access to contraceptive advice and early diagnosis in amenorrhea would cut down abortions to some extent, this is only a stopgap approach to the problem.

The ultimate steps in the prevention of abortion are:

1. Preferential community services to families with children.
2. Maternity leave for employed women.
3. Social and economic aid to unmarried pregnant women and responsible agencies to care for and place illegitimate children.
4. Sex education at all levels correlated with instruction in child care and cultivation of an understanding of the values of parenthood. Many intelligent young people now enter upon life with the negative determination to avoid having too many children but without the positive inclination to have enough. The former position is easily acquired from observation of their elders and discussion among themselves; the latter requires systematic and intelligent presentation by competent teachers.

The author wishes to express her deep appreciation to Dr. William E. Studdiford for his cooperation and encouragement without which this study would not have been possible.

Acknowledgement is also made to Dr. Regine Stix and Mr. Gilbert Beebe for advice in planning the study and to Mr. Murray Geisler for aid in the statistical analysis of the data.



In Fig. 1 is represented the average weight changes during pregnancy and the puerperium in the 2,502 normal pregnancies. As seen in the chart, a few of the patients went beyond the fortieth week of gestation. This is represented by the dotted line. Undoubtedly some of these were due to miscalculation of the last menstrual period. In another study the difference in the weight of the baby in respect to the period of gestation will be presented.

The average weight gain up to the fortieth week of pregnancy was 13.96 kg. This is slightly higher than figures given by other investigators, but may be due to difference in diets, as most of our patients included in their diet one quart of milk per day. Also this gain is calculated from the sixth to the fortieth week and not from the usual weight given by the patient.

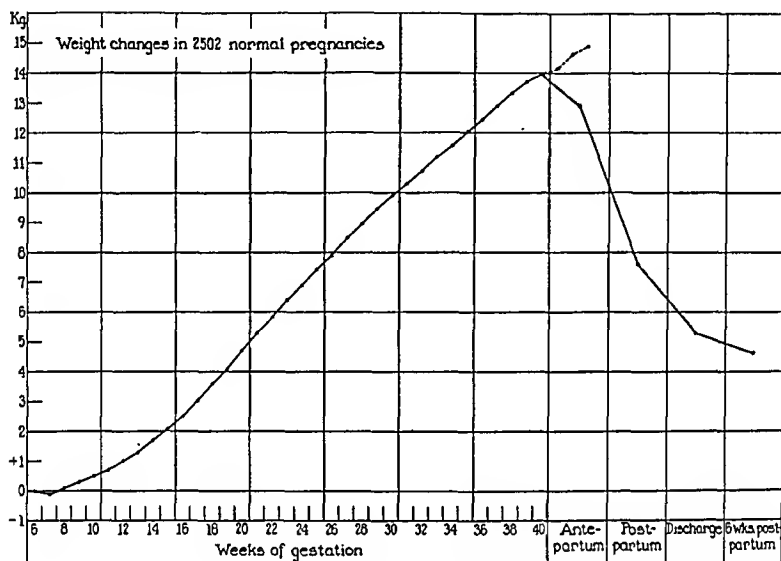


Fig. 1.—Average weight changes during normal pregnancy and puerperium.

During the interval between the last visit to the dispensary and the onset of labor (usually seven to ten days), there was an average loss of 1.11 kg. For convenience, labor is represented in the chart as starting at the fortieth week of gestation. This, of course, was not true in all cases but the change in weight was calculated as the difference between the weight in labor and the last weight in the dispensary. This drop in weight was substantiated by the 35 cases which were followed daily in the hospital.

The average weight loss during delivery was 5.34 kg. If anything, the multiparas lost slightly less than the primiparas. During the first ten days of the puerperium (discharge), there was an additional loss of 2.3 kg. A further loss of 0.68 kg. was sustained until the six weeks post-partum visit. The average weight for six weeks post partum was 60.76 kg., the average for the primiparas being 59.47 kg. and that for the multiparas 62.20 kg., or approximately the same difference as in the usual or nonpregnant weight. They were still above the weight at the onset of pregnancy but were close to the usual weight of 60.52 kg. as given by the multiparas. As a rule, it can be said that the primipara does not return to her usual weight.

Throughout the study of these cases it was noted that the changes in weight were proportional to the original weight of the patient. The heavier the patient at the onset of pregnancy, the more marked the increase in weight. Consequently the weight changes per se are of slight significance unless the original weight of the patient is taken into consideration. This is important, because many heavy patients are unnecessarily placed on restricted diets and treated for toxemia because of what appears to be excessive weight gain, while abnormal weight gain is overlooked in small individuals.

Most of the previous investigations have dealt entirely with total weight changes. It seemed advisable that the normal curve for pregnancy should be determined so that deviations from the normal could be easily detected. Excessive weight gains have been recognized for a long time as indicative of toxemia, while early changes have not always been appreciated because of the lack of standard curves.

In this study we have also had the opportunity of studying the various types of toxemia. Since the investigation was begun before the new classification of toxemia, approved by a special subcommittee of the American Committee on Maternal Welfare, was adopted, an added opportunity was presented to compare the types of toxemia on the basis of weight change.

Moreover, we were particularly interested in devising some method of weight recording that would take into consideration the original weight of the patient. This we find exceedingly necessary, because too often the total weight gain is not evaluated in terms of the size of the patient. In other words, average weight gains mean little in the individual case.

#### DATA

The data are based on a study of 2,935 pregnancies. Many of the patients have been studied through two or more pregnancies. As is our routine practice, these patients were weighed at each antenatal visit, during labor, immediately following delivery, on discharge from the hospital (usually ten to twelve days post partum), and six weeks post partum. Patients are usually seen monthly during the first seven months of gestation, bi-weekly until the last month, when they are seen at weekly intervals. The weights during labor and immediately following delivery are obtained by the use of a special stretcher scale, which permits the patient to be weighed without getting up. Obviously in some of these patients, one or more of these weights were not obtained for various reasons.

In addition, 35 patients were studied daily for a week or more prior to delivery. Most of these patients were in the hospital because of various complications of pregnancy, although some had perfectly normal pregnancies.

The diagnosis of toxemia was based on a complete study which included symptomatology, blood pressure, urine examination, kidney function tests (phenol-sulfonephthalein and urea clearance), blood chemistry, and eye ground examinations. Whenever possible correlation with the new classification will be made. Obviously, the period of observation varied in these patients. Only seven patients were first seen in their sixth week of gestation. The number seen in successive weeks progressively increased until the thirtieth to thirty-second week when they decreased because of premature delivery.

The results will be presented in different groups, namely, normal pregnancy, twin pregnancies, and the various types of toxemia. In all cases the weekly weight gains were calibrated from the recorded data, i.e., it was assumed that the weight gain between two periods of observation was uniform throughout that interval. In the cases of toxemia, this might not have been true if the interval between observations was too long. Moreover, the percentage increase or loss was calculated in each case. This will be discussed later.

*Normal Pregnancy.*—The weight changes in 2,502 normal pregnancies were studied. The usual weight given by these patients was an average of 58.3 kg. It is significant to note that the average usual weight for primiparas (1,227 cases) was 57.3 kg., whereas that for multiparas (1,097 cases) was 60.5 kg. This same difference obtained throughout the subsequent weights. Consequently, no difference in weight changes was noted between the multipara and primipara throughout pregnancy or the puerperium.

TABLE I. WEIGHT CHANGES

WK.	NORMAL				TWINS—NORMAL		TWINS—TOXEMIA	
	% CHANGE	TOTAL WEIGHT	TOTAL WEIGHT	TOTAL WEIGHT	% CHANGE	TOTAL WEIGHT	% CHANGE	TOTAL WEIGHT
6		40.00	60.00	80.00		60.00		60.00
7	-0.12	39.35	59.92	79.90	0.29	60.17		
8	+0.26	40.04	60.07	80.10	-0.48	59.88		
9	0.323	40.17	60.26	80.35	-0.48	59.59	1.27	60.76
10	0.382	40.32	60.49	80.65	-0.69	59.17	0.37	60.98
11	0.404	40.48	60.73	80.97	+0.61	59.53	1.61	61.96
12	0.481	40.67	61.02	81.35	0.21	59.65	-0.85	61.43
13	0.552	40.89	61.35	81.79	0.32	59.84	0.37	61.65
14	0.574	41.12	61.70	82.25	0.32	60.03	0.72	62.09
15	0.674	41.39	62.11	82.80	0.92	60.58	0.91	62.65
16	0.781	41.71	62.59	83.44	0.95	61.15	0.91	63.22
17	0.863	42.06	63.13	84.16	0.95	61.73	0.89	63.78
18	0.905	42.44	63.70	84.92	1.01	62.35	0.91	64.36
19	0.934	42.84	64.29	85.71	0.83	62.86	1.22	65.14
20	0.935	43.24	64.89	86.51	0.77	63.34	0.98	65.77
21	0.905	43.63	65.47	87.29	0.85	63.87	0.73	66.25
22	0.889	44.02	66.05	88.06	0.84	64.40	0.81	66.78
23	0.879	44.40	66.63	88.83	0.78	64.90	0.84	67.34
24	0.830	44.77	67.18	89.56	0.80	65.41	0.79	67.87
25	0.799	45.12	67.71	90.27	0.74	65.89	0.85	68.44
26	0.778	45.47	68.23	90.97	0.65	66.31	0.61	68.85
27	0.830	45.84	68.79	91.72	0.70	66.77	0.75	69.36
28	0.728	46.18	69.29	92.38	0.66	67.21	0.77	69.89
29	0.715	46.51	69.78	93.04	0.63	67.63	0.76	70.42
30	0.658	46.82	70.23	93.65	0.69	68.09	0.62	70.85
31	0.652	47.12	70.68	94.26	0.57	68.47	0.71	71.35
32	0.628	47.41	71.12	94.85	0.66	68.92	0.52	71.72
33	0.658	47.72	71.58	95.47	0.84	69.49	1.00	72.43
34	0.664	48.03	72.05	96.10	0.77	70.02	1.04	73.18
35	0.669	48.35	72.53	96.74	0.64	70.46	1.04	73.94
36	0.615	48.64	72.97	97.33	0.90	71.09	0.47	74.28
37	0.639	48.95	73.43	97.95	0.42	71.38	0.26	74.47
38	0.566	49.22	73.84	98.50	1.08	72.15	1.04	75.24
39	0.424	49.42	74.15	98.91	0.26	72.33	0.77	75.81
40	0.449	49.64	74.48	99.35	0.49	72.68	1.32	76.81
Total	24.10				21.13		28.01	
Labor	-1.58	48.85	73.30	97.78	-1.08	71.89	-0.24	76.62
Delivery	-7.74	45.07	67.62	90.21	11.02	63.96	-12.86	66.76
Discharge	-3.77	43.37	65.07	86.80	-6.92	59.53	-9.15	60.65
6 Wk. P.P.	-1.11	42.88	64.34	85.83	+0.46	59.80	+2.89	62.40

The data to be presented for abnormal pregnancies have all been calculated according to percentage change and, for purpose of comparison, have been standardized for patients weighing 60 kg. at six weeks of gestation.

*Twin Pregnancies.*—Weight studies on 131 twin pregnancies were conducted. Of these, 95 were in normal pregnancies, and 36 in patients with one or another type of toxemia. The weight changes (standardized) are seen in Fig. 3, and the percentage changes are recorded in Table I. The weight gain for normal twin pregnancies was less than normal, namely 21.13 per cent instead of 24.10 per cent. This seems to be due to excessive loss during the early weeks of pregnancy. As expected, the loss during delivery is greater than in single pregnancy. The loss during the first ten days of the puerperium is also excessive, 6.9 per cent or 4.4 kg. Following this, there is an increase during the last five weeks of the puerperium.

The increase in weight in the patients with toxemia was greater than normal, 28.01 per cent, as contrasted with 24.10 per cent for the normal. This increase seems to be concentrated during the early weeks of pregnancy, otherwise the curve is

For this reason, it was felt that the weight changes should be calibrated on the basis of percentage gain or loss, so that comparisons could be made. The percentage change for each week was, therefore, calibrated for the above patients. These data

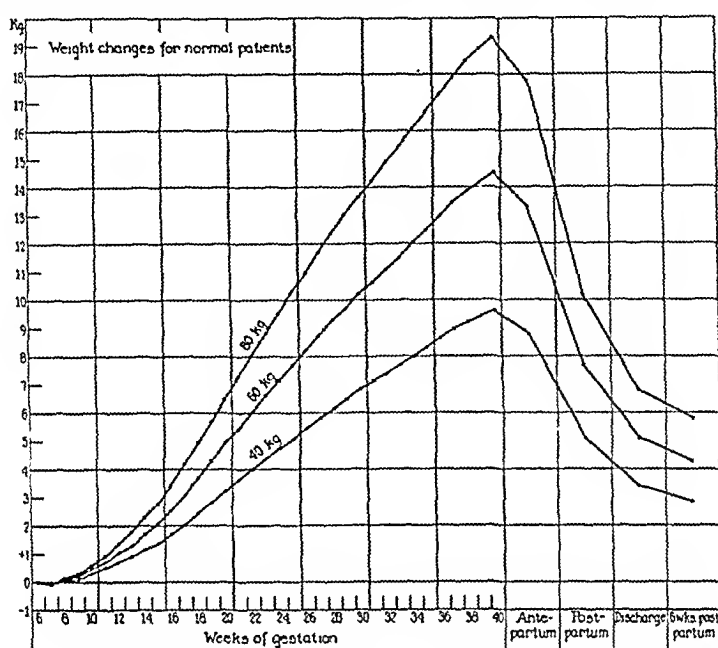


Fig. 2.—Normal weight changes for patients weighing 40, 60, and 80 kilograms.

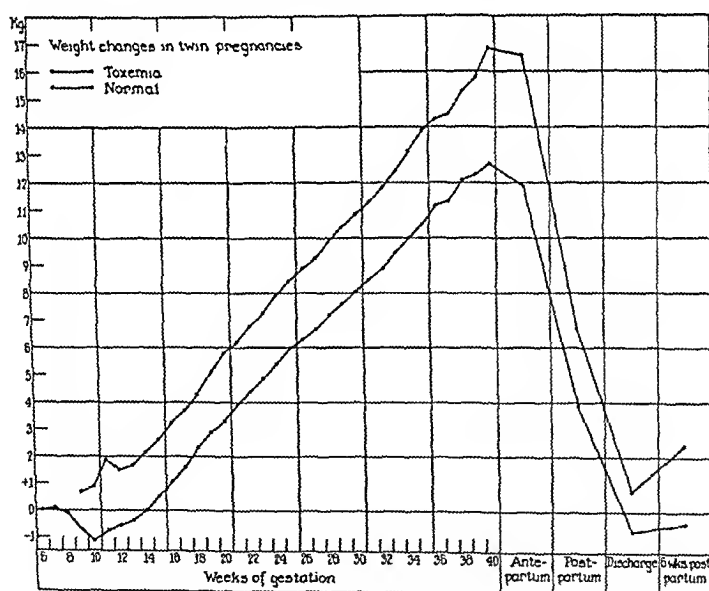


Fig. 3.—Weight changes in twin pregnancy for patients weighing 60 kilograms.

can be seen in the first column of Table I. The percentage increase through the fortieth week of pregnancy was 24.10 per cent. The percentage loss during delivery and the puerperium is also noted in Table I. On this basis, the normal curves for patients weighing 40, 60, and 80 kg., respectively, at six weeks gestation, were constructed and are shown in Fig. 2. Such a chart has now been adapted for use in the antenatal record, so that any changes from normal can be easily detected. For practical purposes the usual weight given by the patient can be regarded as the sixth week weight, and the first recorded weight is placed in its proper spacing. Subsequent changes should conform to the normal curves.

doubtedly to small babies and premature labors. There was a steady loss after delivery so that even at six weeks post partum, the weight was below the original weight. As far as weight was concerned, these patients were definitely worse after the pregnancy. Some of this loss may have been due to edema. These cases would now be classified under renal disease.

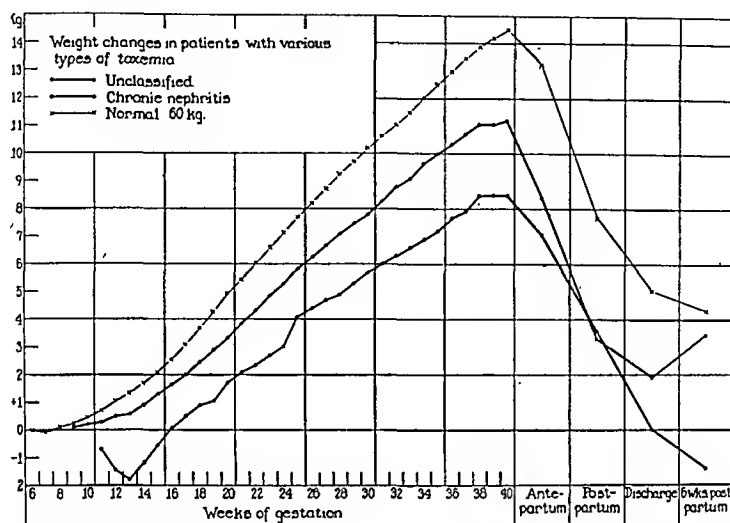


Fig. 4.—Weight changes in certain types of toxemia of pregnancy for patients weighing 60 kilograms.

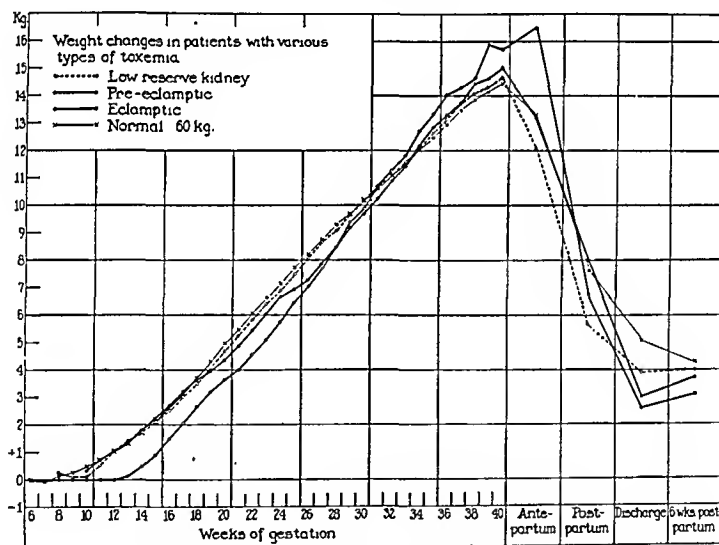


Fig. 5.—Weight changes in certain types of toxemia of pregnancy for patients weighing 60 kilograms.

*Unclassified Toxemia.*—There were 70 patients with unclassified toxemia in this study. In this category, we have included patients in whom a definite diagnosis could not be made. However, it has been our experience, that many of these show definite signs of chronic nephritis in subsequent pregnancies. Also included in this group are many cases which we would now designate hypertensive disease. No definite kidney impairment was detected in any of them.

The weight curve is between normal and that for the chronic nephritic group. Their weight gain was 18.66 per cent. They showed a greater loss just before labor, although the loss during delivery was not excessive, as can be seen in Fig. 4. There was some gain in weight during the latter part of the puerperium. In contrast to

75.20	73.20	71.20	69.20	67.20	65.20	63.20	61.20	59.20	57.20	55.20	53.20	51.20	49.20	47.20	45.20	43.20	41.20	39.20	37.20	35.20	33.20	31.20	29.20	27.20	25.20	23.20	21.20	19.20	17.20	15.20	13.20	11.20	9.20	7.20	5.20	3.20	1.20	-0.80	-2.80	-4.80	-6.80	-8.80	-10.80	-12.80	-14.80	-16.80	-18.80	-20.80	-22.80	-24.80	-26.80	-28.80	-30.80	-32.80	-34.80	-36.80	-38.80	-40.80	-42.80	-44.80	-46.80	-48.80	-50.80	-52.80	-54.80	-56.80	-58.80	-60.80	-62.80	-64.80	-66.80	-68.80	-70.80	-72.80	-74.80	-76.80	-78.80	-80.80	-82.80	-84.80	-86.80	-88.80	-90.80	-92.80	-94.80	-96.80	-98.80	-100.80
75.20	73.20	71.20	69.20	67.20	65.20	63.20	61.20	59.20	57.20	55.20	53.20	51.20	49.20	47.20	45.20	43.20	41.20	39.20	37.20	35.20	33.20	31.20	29.20	27.20	25.20	23.20	21.20	19.20	17.20	15.20	13.20	11.20	9.20	7.20	5.20	3.20	1.20	-0.80	-2.80	-4.80	-6.80	-8.80	-10.80	-12.80	-14.80	-16.80	-18.80	-20.80	-22.80	-24.80	-26.80	-28.80	-30.80	-32.80	-34.80	-36.80	-38.80	-40.80	-42.80	-44.80	-46.80	-48.80	-50.80	-52.80	-54.80	-56.80	-58.80	-60.80	-62.80	-64.80	-66.80	-68.80	-70.80	-72.80	-74.80	-76.80	-78.80	-80.80	-82.80	-84.80	-86.80	-88.80	-90.80	-92.80	-94.80	-96.80	-98.80	-100.80

TOXEMIA

As will be shown presently.

will be discussed separately. As stated above,

l be made whenever possible.

patients with definite

ection tests

*Chronic Nephritis.*—There were 25 patients with definite chronic nephritis, showing the typical changes in kidney function tests and eye ground findings. As expected, their weight gain was below normal, namely 14.50 per cent. There was excessive loss during the early weeks of pregnancy as can be seen in Fig. 4, as compared with the normal curve. Their loss during delivery was below normal, due un-

weeks of pregnancy. This may prove to be a helpful sign in early diagnosis. The total gain was 26.15 per cent. There was an additional gain of 1.1 per cent just before labor. It is during this period that the illness is usually most severe. The loss during delivery is greater, as is also the loss during the early puerperium. The characteristic gain during the late puerperium is noted.

In both the eclamptic and pre-eclamptic patients, individual cases showed rather sudden increases in weight. In Fig. 6, is shown the weight curve of a patient with severe eclampsia, who died shortly after delivery. Autopsy findings confirmed the diagnosis. Convulsions preceded delivery by one day. There had been no marked symptoms prior to this. Contrasted to it is the normal weight curve for a patient of her weight. It can be seen that there were two episodes of increase in weight, one of these early in pregnancy and a second increase in rate of gain about the thirtieth week of pregnancy. Both of these offered early diagnosis. Unfortunately she was not admitted until the day before delivery, and the disease was so overwhelming that delivery had no beneficial effect. The chart does show the importance of recording the weight changes graphically in contrast to normal curves. Early detection of abnormalities can then be made, and it is for that reason that the chart in Fig. 2 is presented for routine use during the antenatal period.

### DISCUSSION

The weight gain during pregnancy is out of proportion to the weight of the products of conception, which approximately account for one-third of the total gain. This excess is undoubtedly mainly due to fluid retention not only in the circulation but also in the tissues. This would indicate that approximately 16 per cent weight increase over the non-pregnant weight is due to fluid. Experiments have already shown that there is about 20 per cent dilution of blood due to hydremia, and it is reasonable to assume that there is an equivalent dilution of the tissue fluids. This is substantiated by the rapid loss during the early puerperium, at a time when the urinary output far exceeds the liquid intake. There is only a slight drop in weight during the late puerperium and most of this is probably accounted for by the involution of the uterus. The loss during delivery (5.34 kg.) can easily be accounted for by the weight of the baby, placenta, amniotic fluid, and blood loss. Moreover, the marked loss in weight following delivery in the patients with toxemia also seems to indicate that the normal process has been accentuated. In these cases we are certain that the water retention is not in the circulating blood (since studies have shown concentration of the blood elements), and yet many of these patients show practically no generalized edema. The atonic and flaccid condition of the tissues also indicates increased tissue fluid.

### SUMMARY AND CONCLUSIONS

A study of the weight changes in 2,935 pregnancies is presented. The average curve for normal pregnancy is shown. Standardized curves of percentage change in weight are presented. This offers an easy method of recording weight changes which allows early recognition of abnormalities and permits comparison of cases. Twin pregnancies as well as the various types of toxemia were studied.

The following conclusions can be drawn.

1. Average weight increase from the sixth to fortieth week of pregnancy was 13.9 kg., or 24.10 per cent.

other forms of toxemia both the chronic nephritis and the unclassified group are definitely below the normal curve.

*Low Reserve Kidney Toxemia.*—The study included 149 cases of low reserve kidney. This group is made up largely of cases now designated as mild pre-eclampsia. A few cases of hypertensive disease would also be included. It should also be remembered in discussing these patients with toxemia that no sharp changes are noted in Fig. 5. This is due to the fact that they are composite charts and do not represent individual cases. The marked changes corresponding to the episode of severe illness varied as to its time of onset; consequently the curve is more uniform than expected. However, we were particularly interested in studying any possible significant change, even prior to the sudden increase in weight. As seen in Fig. 5, all of the toxemias represented in the chart are above the normal curve, except for the early weeks of pregnancy. The types of curve are similar and vary only in degree, which would tend to place them in one type of toxemia. The patients with low

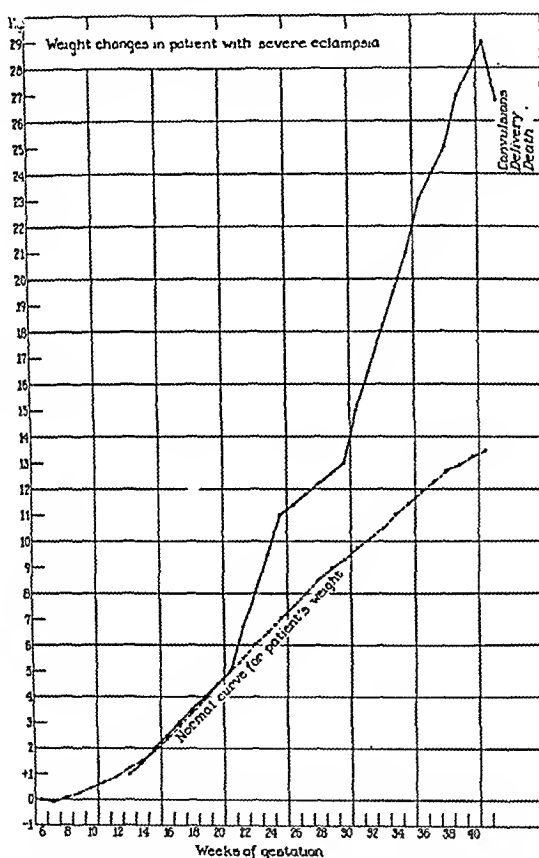


Fig. 6.—Comparison of the weight changes in a patient with eclampsia with the normal curve for her weight.

reserve kidney gained 24.46 per cent or slightly above normal. Their loss before labor, delivery, and puerperium is quite marked, and the gain during the late puerperium is definite. This conforms with the pre-eclamptic and eclamptic cases.

*Pre-eclampsia.*—Weight changes in pre-eclampsia were studied in 28 patients. These cases are definitely those which we would now call severe pre-eclampsia. The changes are practically those mentioned under low reserve kidney. The total gain was 25.15 per cent. They showed more loss in weight during the early puerperium than during delivery. In this respect they simulate the patients with eclampsia. The loss before delivery is less but is compensated for during the early puerperium.

*Eclampsia.*—Thirty cases of definitely proved eclampsia are included in this study. The changes are similar to those already mentioned, except to a greater degree. It is significant to note that there was no weight gain during the early



## A CLINICAL STUDY OF STILBESTROL\*

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**I**N 1934 Cook, Dodds, Hewett, and Lawson reported on the estrogenic activity of some condensed-ring compounds. Following this work, in 1938 Dodds, Goldberg, Lawson, and Robinson described the synthesis of dihydroxydiethyl stilbene, a chemical with marked estrogenic activity. They gave the name of stilbestrol to this new organic compound. Although a most potent estrogen, it is not related chemically nor in any other way to the naturally occurring estrogens. Careful biologic standardization indicates that 1 mg. of this new drug is equivalent in action to 25,000 international units of estrone. Other derivatives of stilbene have varying estrogenic action, but stilbestrol is the most potent of the group. Dodds and his associates, as well as a number of other investigators, have studied the estrogenic action of stilbestrol. These reports indicate that this organic drug will reproduce all the physiologic changes that can be induced by the natural estrogens.

The toxicity of the drug has been studied in laboratory animals and varies widely. Rabbits withstood 30 mg. per kilogram administered intravenously, although cats succumbed to this dosage. Guinea pigs are unusually tolerant of the drug, for they showed no effects from huge doses of 200 mg. per kilo. of body weight. Experiments with the prolonged administration of the drug to laboratory animals are still under way. It is exceedingly important to determine the effect of small and moderate amounts administered at frequent intervals over long periods of time for this mode of administration more nearly simulates the clinical use of the drug.

Loeser administered large amounts of stilbestrol to rats and at autopsy noted changes in the liver, kidneys, and adrenal which he interpreted as manifestations of toxicity. The total dosage that these animals received is not at all comparable to the amounts necessary in the clinical application of this new estrogen. Engle and Crafts recently administered from one to 200 mg. of stilbestrol orally and intramuscularly to monkeys and noted no signs of illness or toxicity. Many other investigators have made careful laboratory and clinical observations for evidence of toxicity with entirely negative results.

When stilbestrol was first administered to patients, nausea with or without vomiting occurred frequently. This gastrointestinal disturbance followed parenteral as well as oral administration. Enteric coating for oral tablets did not eliminate the nausea. In an effort to eradicate this undesirable feature, the drug was given in varying amounts and at different times of the day. It was found that most patients could take a

\*Read at a meeting of the Chicago Gynecological Society, December 15, 1939.

2. The average loss during the week prior to labor was 1.11 kg., or 1.58 per cent.
3. The loss during delivery was 5.35 kg., or 7.74 per cent.
4. Average loss during the first ten days of the puerperium was 2.30 kg., or 3.77 per cent.
5. Further loss of 0.68 kg., or 1.11 per cent, was sustained during the last five weeks of the puerperium.
6. Primiparas as a rule do not return to their original weight following pregnancy.
7. There is no difference in weight changes between the primipara and the multipara.
8. The weight gain in twin pregnancy is not excessive, but the loss during delivery and puerperium is definitely increased.
9. Chronic nephritis and unclassified toxemia show poor weight gain.
10. Low reserve kidney, pre-eclampsia, and eclampsia show similar weight changes, differing only in degree. The total gain is increased, but the loss during delivery and puerperium is excessive. This study would tend to include the three forms under one type.
11. Lack of gain during early pregnancy seems to be a significant sign in the eclamptic toxemias.
12. Weight changes seem to substantiate the new classification of toxemias.
13. The specific weight changes for any woman during normal gestation are proportional to her nonpregnant weight, and for this reason it is essential that weight changes be plotted in such a manner that they may be compared with the normal curves. This may be done by recording the weight changes against the normal weight curves which we have presented for 40, 60, and 80 kg., respectively.

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Perrenoud, J. P.: The Frequency of Double Follicular Rupture. The Duration of the Involution of the Corpus Luteum, *Rev. franç. de gynéc. et d'obst.* 34: 299, 1939.

The autopsy studies of Perrenoud revealed that double rupture of ovarian follicles is not frequent in spite of Samuels' contentions. It occurs about once in every six or eight ovulations. The author found evidence of double ovulation five times in 41 autopsy cases and once in operative cases.

The involution of the corpus luteum usually ends in eight to ten weeks but sometimes it takes much longer when there is no formation of new corpora lutea. The persistence of these old corpora lutea, contrasted often with atrophy of all the organs in general and of the genital tract in particular, indicates that they have one or more important functions in addition to their influence on the uterine mucosa.

J. P. GREENHILL.

Stilbestrol can be administered subcutaneously, orally, and per vaginam. The most striking characteristic is the efficacy of the oral administration of this drug. Leighty and Wiek have just reported that whereas it requires 25 to 30 times the amount of estrone administered orally to reproduce the action of subcutaneous administration, it requires only six times the amount of stilbestrol. Stilbestrol is at least five times as efficacious as the natural estrogen, estrone, when administered orally. The oral administration of this chemical has a prolonged estrogenic action. This property of the drug makes it particularly appealing for use by the clinician. The daily oral administration of a small amount of stilbestrol will maintain a constant blood level of estrin, thereby more nearly duplicating normal conditions. The failure of estrogenic therapy in the past has been due in part to inadequate amounts of the natural estrogens as well as to the difficulties inherent in the mode of administration necessary to provide a constant and adequate blood level.

The clinical use of stilbestrol is indicated in those conditions in which estrogenic medication is desirable. Although our observations have been under way about a year, it has been possible to study only a few conditions carefully.

#### MENOPAUSE

The treatment of the menopause has improved immeasurably since the introduction of endoerinal therapy. Most patients can be given some measure of relief, but there are still many instances where present-day treatment has not provided effective therapy. The most important reason for therapeutic failure is the fact that we do not understand the physiologic mechanism of the climacteric. Obviously, the symptoms of the menopause are brought on by the removal of ovarian influence, naturally or artificially.

The therapy of the menopause by means of estrogens is not considered entirely one of replacement. The gonadotropic principle in the urine is increased following the cessation of cyclic activity in the ovaries. This gonadotropic principle is almost a pure follicle-stimulating substance. Many investigators believe that estrogenic therapy produces its favorable action on the menopausal symptoms by a suppression of gonadotropic hormone production. Heller and Heller recently demonstrated the fact that although estrogens alleviate vasomotor symptoms they fail concurrently to reduce gonadotropic production, for the concentration of this material in the urine does not diminish appreciably under therapy.

The natural estrogens have been used extensively in the therapy of the menopause. In most instances these are administered in oily vehicles intramuscularly or subcutaneously. More recently estriol has been used for oral administration. Estradiol is the most effective and estrone the least effective of the natural estrogens. The amount of the hormone administered varies with the individual. Usually from 2,500 to 5,000 international units a week provides some relief, although in some instances as much as 10,000 to 50,000 units are necessary. The duration of the treatment is adapted to individual needs. Such a therapeutic regime provides moderate relief to the majority of patients; no relief

1 mg. tablet at bedtime without any discomfort. In most patients this amount is sufficient to produce the desired estrogenic action. Larger daily doses of stilbestrol increased the incidence of a gastrointestinal upset, although many patients can tolerate as much as 25 mg. daily without the slightest discomfort. Experiments are under way which we hope will shed some light on the cause and the mechanism of the nausea induced by this medication.

No other undesirable reactions have occurred in the patients on stilbestrol medication. Frequent blood pressure readings revealed no abnormal variations. Urine examinations were consistently negative. There were no evidences of liver damage that could be elicited by careful observation and by the usual tests for impaired function. No dermatoses appeared on any of the women under observation.

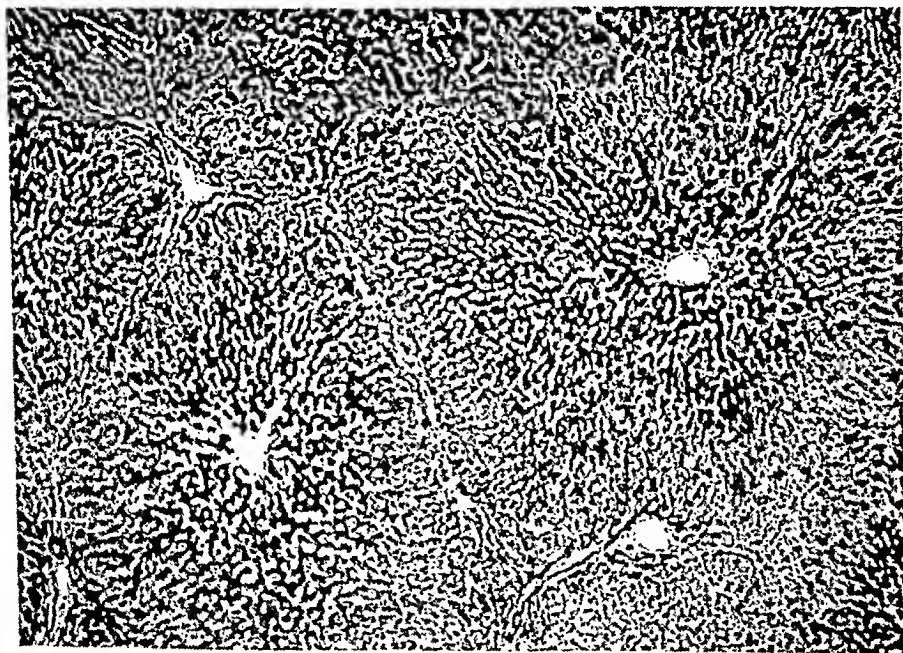


Fig. 1.—A histologic section of the liver of a patient who received 1,125 mg. of stilbestrol in forty-five days, showing no unusual fatty metamorphosis.

It was deemed advisable to make an attempt to evaluate the effects of prolonged administration of stilbestrol in women. Three patients with extensive terminal malignancies were given 10 to 25 mg. of stilbestrol daily. They tolerated the drug exceedingly well and it did not produce undesirable symptoms. These women received a total dosage of 250 mg. in ten days, 350 mg. in thirty-five days, and 1125 mg. in forty-five days, respectively. At autopsy the livers, kidneys, and adrenals were carefully studied (Fig. 1). These organs exhibited no more than the usual changes seen in patients who die after a prolonged illness such as the result of a malignancy. No gross fatty metamorphoses were present in any of these organs. These studies, while not conclusive in any way, confirm the belief that stilbestrol in the moderate doses necessary for clinical administration is not a toxic drug.

volunteered the fact that they felt better than they had in years, that they experienced a sense of well-being and a renewed enthusiasm for living, that they were once more viewing life and its many problems and responsibilities through rose-colored glasses.

In 4 women, only partial relief of menopausal symptoms was obtained. Two of these women took the drug intermittently. In these women the characteristic flushes disappeared completely, but multitudinous complaints persisted and interfered with a complete recovery. These may or may not have been associated with the climacteric.

Twelve women in the group had been treated with the natural estrogens by parenteral administration. For varying periods some of these patients had fairly complete relief from symptoms. The majority of them had little relief but continued on treatment, because it was the best therapy we had to offer. Many a conscientious worker has often questioned how much of the therapeutic result was due to the hypodermic rather than to the estrogen administered. We must admit that it was exceedingly difficult to substitute oral medication for the hypodermic injections, but the striking improvement that followed stilbestrol convinced all but one woman in a very few days that the change in therapy was a desirable one. These women were rapidly freed of all their flushes, and of most of the other concomitant complaints.

There are no definite criteria to indicate the end of the menopause, for this physiologic episode varies considerably in length. When it occurs naturally, it may last from two to four years, for there is no sudden cessation but a gradual waning of ovarian activity. The artificial menopause is induced abruptly following surgery or radiation so that it is shorter in duration, rarely lasting longer than two years. The age of the individual likewise influences the length of the menopause and the severity of the symptoms. Young women are more likely to experience a stormy transitional period (Tables I and II). Medication must be continued until the symptoms begin to wane or disappear. After several months of medication the drug can be reduced, administering 0.5 mg. daily or 1 mg. every other day. In the event that symptoms return, the daily dose can again be increased. It is important to maintain continuous administration of stilbestrol, gradually reducing the amount but not interrupting its administration. A sudden cessation of

TABLE I. ARTIFICIAL MENOPAUSE, K. D. (No. 215115), AGED 49 YEARS

July 6, 1939: Incomplete hysterectomy, bilateral salpingo-oophorectomy (huge fibromyomas).

July 31: Menopausal symptoms for past two weeks, increasing severity, stilbestrol 1 mg. daily, orally.

	HOT FLUSHES	HEAD- ACHES	NERVOUS SYMPTOMS	BLOOD		
				HB	CELL VOLUME %	W.B.C.
July 5	+	-	+	10.7	32	8,100
July 31	++++	++++	++++	Stilbestrol 1 mg. daily		
Aug. 28	-	-	-	12.7	38	6,000
Oct. 4	-	-	-	13.0	39	10,000
Dec. 6	-	-	-	12.9	38	9,100

A résumé of the case history of a patient in whom the menopause was induced artificially at about the time of the normal climacteric. Prompt relief of all the symptoms followed the institution of therapy.

to a considerable number. The mode of administration, the difficulty in maintaining a constant estrogenic level, and the expense of high dosages and prolonged administration have worked to defeat the efficacy of the endocrine treatment of the climacteric.

In evaluating the results of any therapeutic regime in the treatment of the menopause, criteria are exceedingly difficult to select. The climacteric presents such a bizarre picture that few symptoms occur with sufficient regularity to be useful in evaluating results. It is this kaleidoscopic clinical picture that has resulted in the use of many different forms of therapy with good and bad results as the case may be. The most clear-cut symptomatology of the menopause develops in a young woman who has been subjected to an artificial climacteric as a result of surgery or radiation. Here the vasomotor changes predominate. Nervous phenomena and headaches are of secondary importance. Most of these manifestations come on a month to several weeks or more after the cessation of ovarian function. The hot flushes can be used as criteria of the climacteric, for they are pathognomonic. Their amelioration or disappearance is an indication of successful therapy. Nervous phenomena and headaches are less consistent end points.

#### MATERIAL

A selected group of women in the menopause were placed on stilbestrol therapy. These patients had been on careful observation for periods of from three to ten months. They had returned every four weeks for a careful study. The usual pelvic examinations were supplemented by vaginal smears, vaginal and endometrial biopsies, complete blood studies, blood pressure readings, and examinations of the urine. Notations of any untoward complaints or symptoms were made.

Of the 100 women thus studied the menopause had a natural onset in 46, whereas in 54 women it was artificially induced by surgery or radiation. Nine of the women had radiation for the therapy of some pathologic condition. The age of onset of the menopause varied: 16 per cent from 30 to 40 years, 30 per cent from 41 to 45 years, 37 per cent from 46 to 50 years, and 17 per cent from 51 years and over.

Early in this clinical investigation each patient received 5 mg. of stilbestrol daily but this amount was soon reduced to 1 mg. a day, taken at bedtime. It was found that this quantity was sufficient to control all the symptoms of the menopause. About 20 per cent of the women who were receiving 5 mg. of stilbestrol daily complained of nausea with or without vomiting or an uneasy and uncomfortable sensation in the abdomen. When the daily dose was reduced to 1 mg., most of these women could tolerate the medication without any apparent discomfort. In only three instances did the patient object to taking the medication, because the morning nausea and the upset feeling persisted. In a few more instances the patients experienced some nausea for several days after the institution of treatment, but this quickly subsided and did not return.

Ninety-three of the 100 women placed on stilbestrol were completely relieved of their menopausal symptoms. The hot flushes with their concomitant chilly sensations and uncomfortable sweats often disappeared within seventy-two hours following the onset of treatment. The relief was so rapid and so complete that many women expressed amazement at the result. Although the hot flushes were used as criteria of the menopause and their disappearance as a guide to effective treatment, other characteristic menopausal symptoms likewise disappeared. Headaches and the peculiar tenseness that develops at the back of the head and neck muscles disappeared or were improved. Nervous manifestations and the hyperexcitability and irritability characteristic of the climacteric were relieved. The mental depression that often develops was likewise improved. Many patients

Except for the fact that such bleeding after an interval of amenorrhea is disturbing to the patient, it is of no significance. Irregular periods of bleeding at the menopause always deserve the most careful scrutiny and investigation by the clinician.

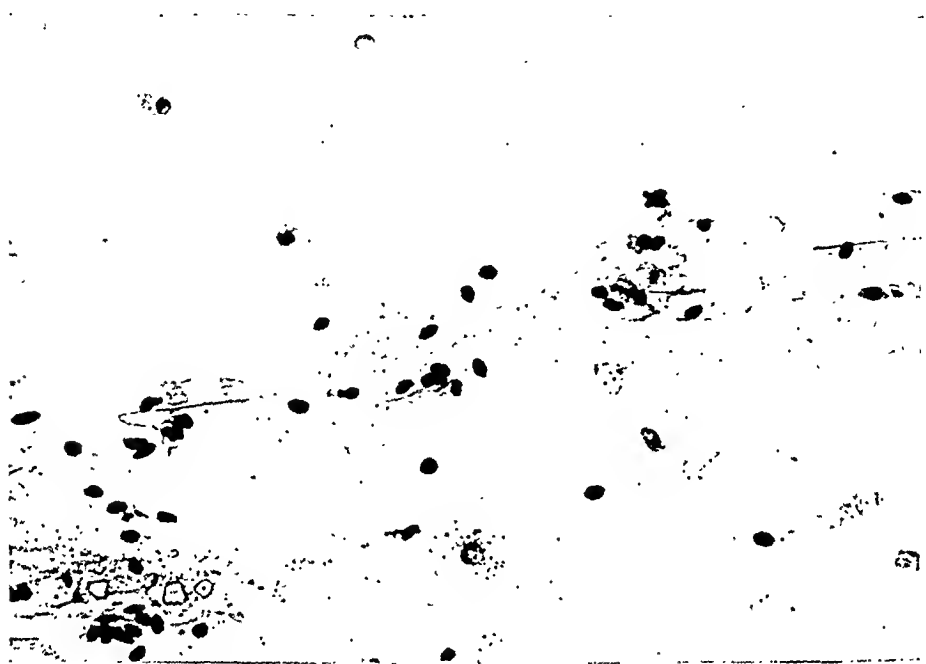


Fig. 2.—The vaginal smear on a patient in the late menopause, showing the characteristic cellular content.

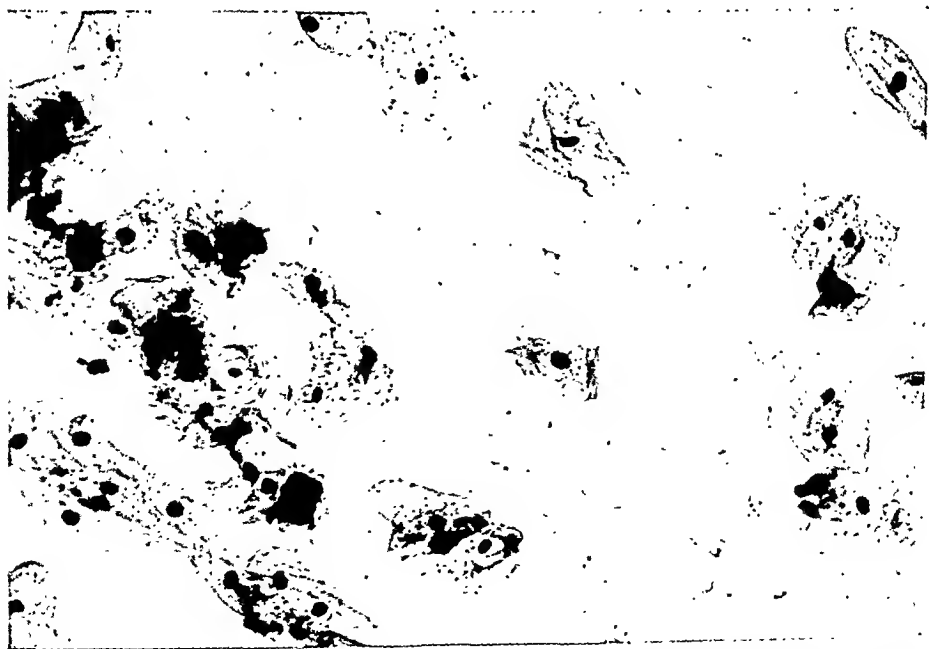


Fig. 3.—A vaginal smear on the same patient four weeks after the onset of stilbestrol therapy showing the characteristic change in the cellular content of the vagina. The large desquamated cells are rich in glycogen.

TABLE II. ARTIFICIAL MENOPAUSE, P. W. (No. 217823), AGED 21 YEARS

1938: Left cyst-oophorectomy  
 1939: May, right cyst-oophorectomy for huge cystadenoma  
 Menopausal symptoms began in June, increasing severity  
 Stilbestrol 1 mg. daily, orally, October 10

	HOT FLUSHES	HEADACHES	NERVOUS SYMPTOMS
Oct. 10	4	+	+++
11	8	+	++
12	5	-	++
13	4		+
14	8		
15	8		
16	5		
20	2		
24	0		

Feels fine, no symptoms, better than in years

A résumé of the treatment of an artificially induced menopause in a young woman. Although there was an immediate response following the onset of therapy, complete relief was not obtained for a period of about ten days. Since that time she has had no menopausal complaints.

therapy is often followed by bleeding within a period of ten to twenty days. This is the characteristic withdrawal phenomenon.

Objective criteria can be used to determine the efficacy of treatment. The vaginal mucosa is an excellent indicator of estrogenic action in the human female. The author has previously called attention to changes which take place in vaginal mucosa following the cessation of ovarian activity. These changes consist of a gradual thinning of the mucosa and a change in the cellular content of the squamous epithelium. The large cells of the upper layers rich in glycogen completely disappear and are replaced by smaller inactive cells. These vaginal changes can be seen on gross examination, in small biopsies of the vaginal mucosa or in the cellular character of the vaginal smear. Papanicolaou and Shorr correlated the relief menopausal symptoms and the estrogenic changes induced in the vaginal smear (Figs. 2 and 3).

Several interesting observations were made in the therapy of these women. Many of the patients complained of breast changes following the institution of therapy. The patients developed a sense of tightness and fullness in their breasts, such as they had previously experienced in early pregnancy. They actually increased in size and became sensitive to the usual clothing. The nipples became more prominent and likewise sensitive. Some increased pigmentation of the nipples and the areolae made both of these structures more prominent. This initial breast discomfort usually disappeared on continued medication or on a reduction of the daily dose. Prolonged medication resulted in no further breast changes.

The interruption of treatment for a week or longer occasionally resulted in vaginal bleeding which persisted for several days or longer. This is the well-known estrin withdrawal phenomenon. An endometrial biopsy at this time revealed a moderate endometrial proliferation as a result of the estrogenic medication. Continued administration of stilbestrol does not result in continued proliferation of the endometrium.



## PRIMARY AMENORRHEA

The onset of menstruation or puberty heralds the advent of adolescence and sexual maturity. Normal physical feminine development and the capacity for reproduction depend on normal reproductive organs which function as a result of a closely correlated endocrinal relationship. In some young women menstruation fails to take place. Although this failure is only one manifestation of an abnormal reproductive mechanism, it provides the name of primary amenorrhea.

The absence of the menses in a young woman may be the result of a lack of normal development of all or a part of the reproductive tract. The uterus may be underdeveloped, rudimentary, or its canal non-patent. The vagina may be absent or its lumen fail to provide continuity with the uterus. The gonads may be absent or abnormal. The menstrual function may be absent because of an endocrinal failure, pituitary or ovarian in origin. The anterior lobe of the pituitary provides the motor for the cyclical changes which take place in the reproductive organs. Pathologic conditions in the pituitary gland may hold these changes in abeyance or completely inhibit them. The ovaries may not be responsive to normal pituitary stimuli because of abnormal development, thereby resulting in uterine inactivity. It may be possible to determine which of these three factors operate in an individual with primary amenorrhea. It may or may not be possible to correct or remove the cause.

A lack of normal development of the sex function may have a profound effect on the physical, psychic, and even mental development of the young woman. In some of these individuals puberty and the changes it initiates are delayed into adulthood. Thus the bony skeleton may fail to develop normally as a result of delayed epiphyseal closures, secondary sex characters which differentiate the woman from the sexless child may all be absent, and the normal feminine figure fails to evolve. Associated with this lack of physical development, there usually occurs a lack of psychic development resulting in an abnormal social adjustment. The young woman may begin to brood over her physical and sexual inequalities. She magnifies their importance to such an extent that she develops an inferiority complex, a temporary or permanent psychosis, or abnormal sex relationships. Menstruation, therefore, although only one index of functioning reproductive organs, becomes of paramount importance to these individuals with primary amenorrhea.

Obviously, in the presence of only rudimentary portions of the Müllerian derivatives or in their complete absence, vaginal bleeding is impossible. When a lack of normal development of these organs is present or an abnormal endocrinal relationship interferes with normal sex activity, improvement and perhaps a restoration to the normal is, theoretically at least, possible. Every advance in endocrinology has offered one more challenge to find a solution to some of these interesting problems.

Theoretically at least, in many of the patients with primary amenorrhea, gonadotropic substances which supplant the action of the normal anterior lobe of the pituitary gland should prove efficacious. These

Several of the women described an increased libido after a gradual waning for a number of years. This may have been induced by the return to normalcy of the vaginal mucosa with a resultant improvement in coitus.

A careful study of the blood findings in this group of women revealed no detrimental effects as a result of the therapy. The white blood cells remained stationary in number or varied in such small ranges as to be statistically insignificant. Cytologic studies revealed no abnormal changes in the number or character of the cells. The cell volume and the hemoglobin were unchanged in most of the patients under observation. In a small group of women with marked anemias of long standing, surprising improvement occurred after short periods of stilbestrol therapy. The increase in cell volume and hemoglobin were proportionate and of such a marked degree as to be especially noteworthy (Table III). We hesitate to ascribe these changes to stilbestrol, for several factors which could influence the blood findings entered into most of these patients under observation. Nevertheless, this observation is so striking that we are giving it further study. One can at least conclude that stilbestrol in the amounts used for clinical therapy does not influence the blood constituents.

TABLE III. THE BLOOD FINDINGS IN SEVERAL PATIENTS TREATED WITH STILBESTROL, SHOWING THE MARKED RISE IN HEMOGLOBIN AND CELL VOLUME

PATHOLOGY	MENOPAUSE INDUCED	THERAPY	DATE	HB. GM.	CELL V.	W.B.C.
Croll (213970), Aged 38 Years						
Endometriosis Little bleeding	Radiation 2/26	Began stilbestrol May 22, 1 mg. daily No other therapy	2/ 1	8.3		9,000
			2/23	9.2	26%	9,400
			5/20	9.0	29%	11,000
			7/12	12.8	40%	
			10/ 2	14.0	42%	5,000
Koskonski (216213), Aged 45 Years						
Large endo- metrial polyp	Hysterectomy Bilat. salp. ooph.	Stilbestrol 6/5 5 mg. every other day	3/ 9	10.0	34%	9,300
			4/28	10.0	32%	9,850
			5/10			10,200
			6/ 3	9.1	30.5%	4,130
			8/11	13.0	42%	9,300
			9/22	13.8	43%	10,700
			10/20			10,000
			11/17			9,200
Tanneberger (206673), Aged 43 Years						
Fibroids Profuse menses  Transfusions 650 c.c. 550 c.c.	10/22/38 Hysterectomy Bilat. salp. ooph.  10/21 10/26	Stilbestrol 4/13 5 mg. every other day	1938			
			9/29	6.6	26%	8,200
			10/20	6.2	25%	
			10/22	7.9	29%	
			10/24	8.0	23%	
			10/28	8.5	30%	7,800
			1939			
			4/13	10.9	35%	
			9/ 8	13.8	40%	
						6,300

moderate anemia at the onset of therapy, 8.8 Gm. Hb., cell volume 25 per cent, which has corrected itself so that at present the Hb. is 13.8 and cell volume 41 per cent. Monthly studies revealed little fluctuation in white blood count, averaging approximately 8,000. Other laboratory examinations have been negative.

Marked physical changes have taken place as demonstrated by the illustrations (Figs. 4 and 5), the most gratifying to the patient being the occurrence of bleeding. A pinkish discharge occurred May 22, 23, and 24 and periods have occurred during June, August, September, and November. Most of these periods occurred even with continued use of stilbestrol, although the September period was provoked by withdrawal of the drug for two weeks. The flow has been moderate lasting from three to five days. Biopsies revealed a moderate proliferative phase of the endometrium.

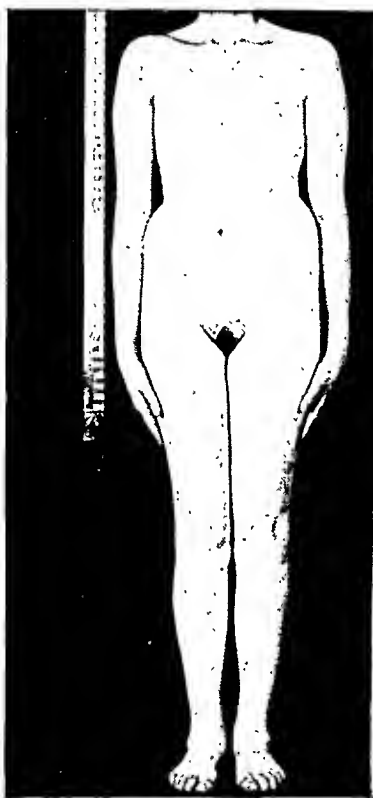


Fig. 4.



Fig. 5.

Fig. 4.—S. B. (Unit No. 150466). Before the onset of stilbestrol therapy. Note the lack of breast development, the small pale nonpigmented nipples and areolae, the scant growth of pubic hair, and the general juvenile appearance.

Fig. 5.—S. B. (Unit No. 150466). The young woman has been on 1.0 mg. stilbestrol daily for four months. Note the breast development as well as the nipple growth and the marked pigmentation of the nipples and areolae. There is likewise an increased pigmentation of the lineae abdominalis. A thick growth of pubic hair has occurred. There has been a marked change in the general physical appearance of the patient.

The patient developed the typical mature feminine figure, the angular appearance disappeared and a luxuriant growth of hair over the pubis and under the axillae appeared. The breasts have enlarged and the nipples have increased in size, with pigmentation of the areolae and nipples. Pigmentation is also present in the lineae of the abdomen and other areas. The external genitalia have reached the stage of normal adult sex development. The vagina has increased in roominess and length, with prominent rugae. Biopsy reveals many layers of cells in the squamous epithelium. The uterus has increased to approximately normal size, with a normal ma-

gonadotropes should stimulate the ovaries to normal cyclical activity so that these structures can produce the hormones necessary for endometrial growth, secretion, and menstruation. Impure gonadotropes from pregnancy urine and from gland extracts have little effect on the human ovary. Equine gonadotrope more nearly reproduces the action of the normal pituitary gland and is the most potent of our gonadotropic principles. Some results have been obtained in the treatment of primary amenorrhea, but in the majority of patients treatment with pregnant mare serum has been unsuccessful. It is possible that the ovaries of these women are primarily at fault. They may be so abnormal or undifferentiated that they are refractory to stimulation by the pituitary gland, in which event gonadotropic therapy is doomed to failure.

Estrogens must be considered as purely substitution therapy. The natural estrogens can bring about the development of the reproductive organs, the breasts, and the secondary sex characters. To accomplish this, estrogens must be administered in comparatively huge doses intramuscularly, and at frequent intervals, to maintain a constant level of blood estrogens. On the withdrawal of this hormone retrogressive changes begin, so that after a short time the structures revert to almost their previous state.

Stilbestrol has provided one ideal estrogen for the treatment of this condition. The daily oral administration of a small amount provides a sufficient estrogenic stimulus to produce physical and sexual maturity of these underdeveloped young women. The changes induced in these patients in a short period of a month or more are truly astounding. The following two case reports illustrate the profound changes that can take place on stilbestrol medication.

CASE 1.—S. B. (Unit No. 150466) was 21 years of age. When this patient was 18 years old (1936) she was admitted to our clinics never having menstruated. She has been under observation since 1934, during which time she received endocrinal substances. During 1936 and 1937 she was given various gonadotropic preparations, including, in 1938, the natural estrogens in doses from 20,000 to 100,000 units at a single administration preceding the use of mare serum hormone. No vaginal bleeding nor pronounced change in physical development occurred. Some growth of the reproductive organs appeared.

Her early history was negative. She developed a sparse growth of pubic and axillary hair at the age of 11. When 16, she became concerned over her lack of menses. She presented the typical picture of primary amenorrhea, was typically feminine in type, but retained the prepubertal characteristics, square shoulders, narrow box-like hips, and android pelvis. Her appearance was juvenile. X-rays revealed normal epiphyseal growth with retardation of closures in the proximal phalanges. The sella turcica was normal. The visual fields were normal. The basal metabolic rate varied from -9 to -17. The breasts were hardly visible and could not be demarcated except for rudimentary nipples. The flattened pale pink areolae measured 8 mm. in diameter. Pubic hair was sparse and silky. The labia majora were flat and hardly evident; the labia minora were thin and almost transparent. The vagina was narrow, admitting the finger with difficulty, and there were no palpable rugae. The uterus was infantile in type, with a large cervix and a small corpus.

She was placed on stilbestrol on May 1 and has continued taking 1 mg. daily by mouth, with but few periods of rest. She tolerated the drug well. She had a

of occasional nausea on arising. Blood examinations varied little during therapy. Hemoglobin averaged from 13 to 14 Gm., cell volume 37 to 42 per cent and white blood cells about 6,000. (Figs. 6 and 7.)

She improved markedly during a four months' period. Her first flow occurred July 1, lasting two days. She bled for eight days in August, two in September, and five in October. These periods occurred in spite of continuous therapy. Four biopsies were obtained on the first day of each flow with little endometrial variation from moderate proliferation. Prior to therapy no endometrium could be obtained. The external genitalia assumed the normal adult type. The vagina increased in diameter, and the vaginal mucosa assumed the normal adult type. A faint bluish discoloration is evident in the mucous membranes of the vagina and cervix. The corpus grew in size and length. Pubic and axillary hair grew markedly. The breasts increased in size and now stand out prominently from the chest wall. The nipples increased in size and prominence with marked pigmentation. Small areas of pigmentation on the body are more pronounced.

The patient has improved mentally, becoming cheerful, happy, and feeling as if she is a normal individual. This psychologic change is most important to the well-being of this individual.

#### DISCUSSION

Many interesting observations have been made in the treatment of this group of patients. Stilbestrol completely replaces the estrogenic activity of the ovary. It produces sexual maturity in the immature female with the exception of ovarian function. The prepubertal state is rapidly replaced by the physical and organic development of the mature woman. All of the secondary sex characters develop. The reproductive organs assume the normal adult type. The undifferentiated juvenile physical characteristics give way to the mature feminine form. The speed of the transition is remarkable, for all this is accomplished in a period of several months, whereas normal adolescence requires three or four years. The gonads are the only reproductive organs that are not affected and remain dormant.

It was possible to produce some of these changes by means of the natural estrogens when they were administered at frequent intervals and in large doses. It has not been possible to produce the degree of physical and sex development seen in this group of women. Furthermore, it has been impossible to maintain the development for long periods of time so that the patient would be benefited by the change. The natural estrogens were administered intramuscularly at varying intervals and for short periods of time. This mode of medication probably resulted in varying concentrations of blood estrogens not conducive to optimum results. Oral medication can be easily maintained over long periods of time, thereby producing a constant estrogen level in the blood and tissues.

Obviously, this substitution therapy must continue in order that these young women remain normal. When natural estrogens only were available, continued therapy was impossible and undesirable. Now that it is possible to take a small tablet once a day or less often, prolonged substitution becomes entirely feasible. There can be no question as to the desirability of continued therapy in these young women, providing this therapy is safe and no injurious effects occur. Only careful clinical observations and experimental studies over long periods of time will answer these questions. No one doubts the wisdom of continued sub-

ture ratio between the corpus and cervix. Psychic changes have been phenomenal. The patient had been morose, unhappy, and a defeatist, but after treatment began a marked change took place in these respects. With a renewed interest in life her whole demeanor has changed, and she is now a normal healthy young woman who works hard and enjoys social relaxations.

CASE 2.—R. F. (Unit No. 219149), aged 25 years, was admitted to our clinics early in 1939 for primary amenorrhea. She had been treated elsewhere for two years. Thyroid, estrogenic hormones, and anterior pituitarylike substance had proved ineffective.

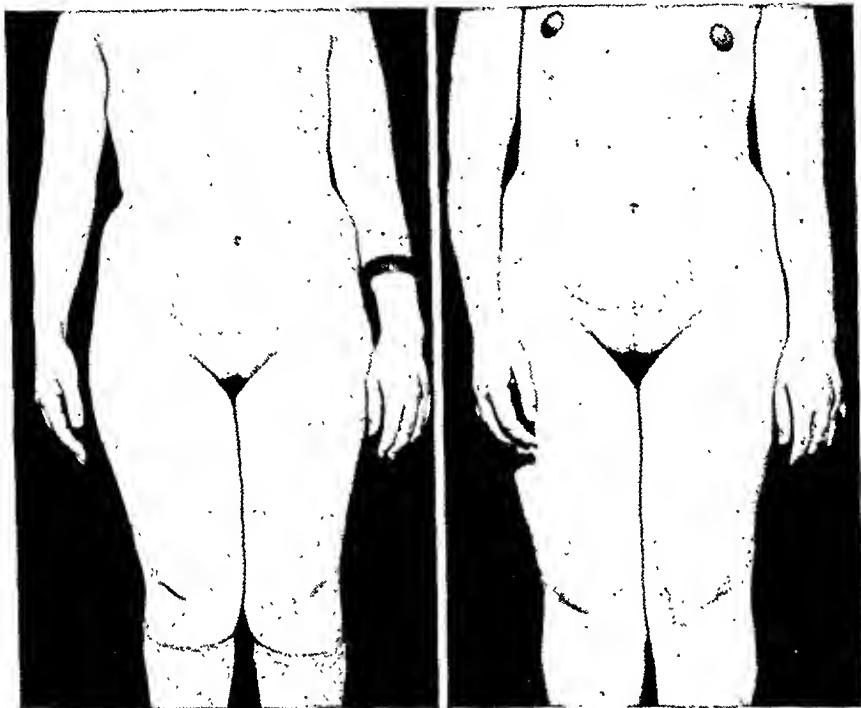


Fig. 6.

Fig. 7.

Fig. 6.—R. F. (Unit No. 219149). Before the onset of stilbestrol therapy. The lack of breast development and the scant growth of pubic hair is particularly well shown in this photograph.

Fig. 7.—R. F. (Unit No. 219149). This young woman has been on 1.0 mg. stilbestrol daily for three months. There has been a marked enlargement of the breasts including marked growth of the nipples. The pigmentation of the nipples and the areolae is particularly striking. Note likewise the increased pigmentation of many small localized areas which were hardly evident prior to therapy. The increased pigmentation of the lineae abdominalis is likewise striking. There has been a marked growth of pubic hair.

Her early history was negative, except that she was a premature baby. Growth ceased at 15 or 16 years of age. Her appearance was typically feminine, but she had retained juvenile characteristics. X-rays revealed well-advanced epiphyseal closures. The sella turcica was small. A constriction of the visual field was present, but there were evidences of a pathologic pituitary gland. Basal metabolic rate was -7. The breasts were neither visible nor palpable. The nipples were tiny and the areolae small. The pubic and axillary hair was scant. The external genitalia were underdeveloped. The labia majora were flattened and the labia minora thin and of tissue paper consistency. The vagina admitted one finger with difficulty, the vaginal walls were smooth and shiny. The uterus was smaller than normal, consisting predominantly of cervix.

She was placed on 2 mg. of stilbestrol daily, orally in June, but this amount was reduced in several weeks to 1 mg. She tolerated it well at first, but later complained

desquamated endometrial fragments. The character of these periodic bleedings provides additional evidence as to the fundamental physiologic mechanism underlying normal menstruation.

The development of the breasts is limited to a growth of the duct system. No changes take place in the secretory acini, for these are not stimulated by the estrogens. The nipple and the areolae show pronounced growth changes. No secretion is present in these breasts.

The pigmentation that occurs is most marked in the nipples and the areolae, but the linea alba as well as other mildly pigmented areas become intensely discolored. As the treatment is continued, these pigmented areas increase in intensity. This unusual pigment response is much greater in degree than that usually seen in normal pregnancy. The natural estrogens provoke pigmentation, but not in the degree seen in these patients. We are conducting studies into the nature of this pigmentation.

### CONCLUSIONS

Stilbestrol, a new synthetic estrogen unrelated to the natural estrogens, has tremendous clinical possibilities. The oral administration of the drug can reproduce all the changes induced by the natural estrogens much more effectively and to a greater degree. It replaces the estrogenic action of the ovary. Many clinical conditions which are the result of a deficient ovarian activity or its complete cessation can now be easily and successfully treated. The treatment of the menopause and primary amenorrhea with stilbestrol is discussed in this paper. Other conditions under treatment at the present time will be discussed at a later date.

The widespread clinical use of stilbestrol must await more adequate evidence as to its possible toxicity. Pharmacologic experiments involving the long-continued administration of moderate amounts of this drug must be carried out to determine late undesirable effects. Careful clinical observations must be continued with the most guarded approach until such time as the lack of toxicity of the drug can be firmly established.

The author wishes to express his thanks to Dr. Anderson and Dr. Morrell of E. R. Squibb and Sons and to the Winthrop Chemical Company for their generous supplies of stilbestrol.

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### DISCUSSION

DR. FRED L. ADAIR.—I do not believe we should accept this very potent agent for general clinical use until we know more about its benefits and more about its abuses. We find doses of  $\frac{1}{2}$  mg. or 1 mg. highly effective in controlling menopausal

stitution therapy in hypothyroidism, in diabetes, and in other glandular deficiencies. Why should one doubt the wisdom of continued therapy in hypo-ovarianism?

The amount of stilbestrol necessary to maintain the optimum development of the individual is difficult to ascertain. Larger amounts of the drug are necessary during the transitional period, but small amounts may suffice to retain the desired changes. About 1 mg. daily has been sufficient to prevent any regression, and it is entirely possible that this amount is too large. Careful endocrinal assays may reveal the optimum daily consumption of this drug. Nature is very lavish in the production of its own endocrines, and much of the excess is destroyed or eliminated. Substitution therapy need not be that extravagant.

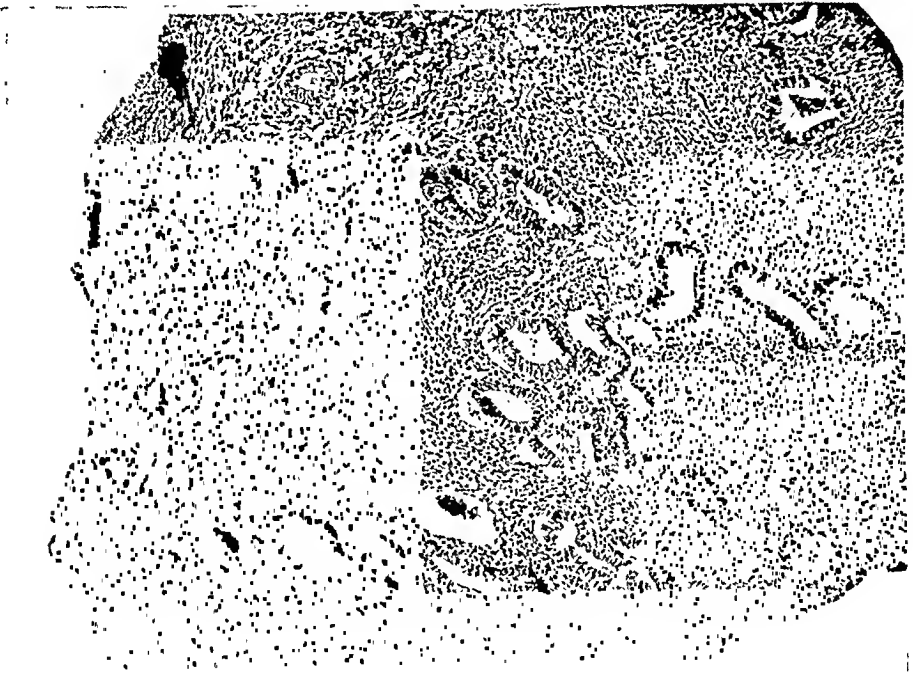


Fig. 8.—A biopsy of the endometrium obtained on August 15, the first day of an anovulatory menstrual flow which lasted eight days. A moderate proliferation of the endometrium is present which is representative of the endometrial picture of this group of women with primary amenorrhea who are under treatment with stilbestrol.

Periods of bleeding occur seven to twenty days following the sudden withdrawal of the drug as well as on continued medication. These periodic bleedings occur with some degree of regularity. The only difference between true ovulatory menstruation and these anovulatory bleedings is in the endometrial picture. The mucosa of the uterus develops a moderate proliferative phase (Fig. 8). Continued medication with stilbestrol does not result in continued proliferation of the endometrium. The endometrial picture resembles that normally encountered prior to ovulation. The bleeding is preceded by the usual premenstrual prodromas, and subjectively these periods are very much like normal menses. The blood loss is scant in amount and there is no loss of



## HYPERTHYROIDISM AND PREGNANCY\*

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AS HYPERTHYROIDISM is a rare complication of pregnancy, the experience of most obstetricians is limited to a few cases. It is perhaps for this reason that one finds in the literature such marked disagreement as to treatment, as is evidenced by the varied opinions relative to the use of iodine, surgery of the thyroid gland during pregnancy, continuation of the pregnancy, and therapeutic abortion.

In the Woman's Clinic of the New York Hospital in the past seven years, 18 cases of hyperthyroidism complicated by pregnancy were noted in 23,439 patients, an incidence of only 0.076 per cent. Clinically these cases were divided into diffuse exophthalmic goiter (12 cases), adenomatous goiter (4 cases), and hyperthyroidism without excessive goiter (2 cases). The symptoms of hyperthyroidism were the same as for nonpregnant women, and need not be given here. The symptoms antedated pregnancy in 10 cases, while 8 patients developed symptoms during the pregnancy, and in the latter group were 3 private patients in whom the symptoms were thought to have been precipitated by the knowledge of pregnancy. Only 1 patient could date symptoms to a previous pregnancy, and another patient had been subjected to two thyroid operations without relief. The thyrotoxicosis was regarded as severe in 5 cases (3 having a nodular goiter), moderately severe in 9 cases, and mild in 4 cases. The average duration of symptoms was 3.2 years before the current pregnancy.

TABLE I. THE AVERAGE DURATION OF PREGNANCY IN 18 CASES OF HYPERTHYROIDISM

NUMBER OF CASES	
40 weeks	10
37 weeks	3
Abortions	5
Total	18

The average duration of pregnancy in the 18 patients is shown in Table I. Of the 5 abortions, 4 were performed for therapeutic reasons, 22.2 per cent, while one occurred spontaneously. The majority were delivered at term.

The average age was 31.6 years, which is nearly eight years older than the average for the clinic population. There were 12 multiparas and 6 primiparas, with an average number of 2.6 pregnancies (including abortions) for each patient. Hinton gives a higher incidence in primiparas, while Portis and Roth found a higher incidence in multiparas.

\*Read at the Section of Obstetrics and Gynecology, New York Academy of Medicine, December 26, 1939; and read in part at the Graduate Fortnight of the Academy at the New York Hospital on October 26, 1939.

symptoms but we must not necessarily assume that that is the proper dose for a woman with amenorrhea or for a woman in whom suppression of lactation is desired.

I wish to call attention to two observations made by Dr. Davis. The first is the effect it has on the pigmented cells. There is nothing known regarding what effect stilbestrol will have on such cells and we should be very careful with its administration in a patient with pigmented moles because little is known about its stimulating effect. The second is the stimulation of the hematopoietic cells with increased hemoglobin. It would seem with this observation that if the drug is irritating to these cells there might be some stimulation and an overdosage would be harmful. Studies are being carried out in regard to the effects of the administration of the drug on the liver and hematopoietic system. We are attempting to study this drug by very carefully controlled experiments.

DR. PHILIP F. SCHNEIDER.—The question of the toxicity of stilbestrol is of importance from the standpoint of safety as well as economy. The criticism of toxicity as manifested by nausea and more recently the claim of retention of bilirubin have been presented. Sevringhaus, Davis and others have discounted this criticism by the observation that nausea has disappeared by reduction of dosage. This would suggest the possibility that clinical evidence of toxicity as well as experimental evidence of retention of bilirubin may be due to excessive dosage rather than to inherent toxicity of the preparation.

Control of estrogenic therapy by means of vaginal smears, using the technique of Papanicolaou in menstrual, reproductive as well as menopausal conditions in our experience would seem to substantiate the above conclusions.

Until the factor of toxicity is more definitely repudiated by more additional evidence it seems obvious that this particular synthetic estrogenic preparation should be used with extreme caution.

DR. DAVIS (closing).—The most important problem presented is the possible toxicity of this new drug. We have treated almost 200 patients for varying lengths of time, many for almost a year. The absence of all symptoms or signs indicative of toxicity, the absence of skin rashes and of neurological symptoms were, indeed, surprising, in view of some of the published reports. The outstanding thing in the therapy of these patients was the absence of all undesirable reactions.

Few patients complain of nausea when the daily dose of the drug is 1 mg. or less. In a number of instances the nausea which was present during the first few days of the administration disappeared on the continued use of the therapy. The usual estrin withdrawal bleeding can be readily induced by stilbestrol medication. However, in some of the patients under continued therapy, periods of bleeding occurred in spite of the constant estrin level. The endometrial changes were the same in both instances.

Obviously, in the treatment of primary amenorrhea the use of an estrogenic substance is entirely substitution therapy. In order to maintain the desirable changes induced by continued administration of this preparation, these young women would have to take the drug until they are 40 or 45 years old. If this drug is found to be nontoxic, this is not objectionable. In all endocrine deficiencies, only substitution therapy is available. Hypothyroidism has to be treated indefinitely. There is no reason to feel that one can cure hypogonadism by means of estrogenic medication. Continued medication would be desirable for these girls benefit tremendously by such therapy. Their entire outlook on life becomes changed. Their work improves and they gain renewed interest in living.

The type of delivery is shown in Table III and one sees that 10 cases, or 76.9 per cent, had a spontaneous delivery. Of the operative cases, cesarean section was performed for placenta previa, low forceps were applied for fetal distress, and a Voorhees' bag was inserted to initiate labor because of toxemia. The average duration of labor was sixteen hours.

TABLE IV. THE TYPES OF ANESTHESIA USED FOR DELIVERY OR TERMINATION OF THE PREGNANCY

	NUMBER OF CASES
Nitrous oxide, oxygen, ether	12
Cyclopropane	2
Local infiltration	2
Avertin	1
No anesthesia	1
Total	18

The types of anesthesia used for delivery or for the termination of pregnancy are given in Table IV. Nitrous oxide, oxygen, and ether mixture was administered to two-thirds of the patients. Since the duration of the anesthesia was short (the majority of the patients being multiparas) ill effects from the nitrous oxide were not anticipated. Morphine and scopolamine, or rectal ether analgesia, was used during labor in only 6 patients.

The average weight of the infants was 3,495 Gm. (7 pounds, 11 ounces), which agrees with the average weight of infants in the clinic. There was no fetal mortality in babies weighing 1,500 Gm. and over.

The puerperium was mildly febrile in 2 cases. There was a questionable thyroid crisis immediately after delivery in 1 case. Lactation occurred normally in 7 patients and was permitted in these. There was no maternal mortality.

#### TREATMENT

Iodine in the form of Lugol's solution or syrup of hydriotic acid was used in all but 4 of the cases in which therapeutic abortion was performed. An appreciable lowering of the basal metabolic rate was observed following iodine therapy, as shown in Fig. 1. A similar decrease has been observed by Mussey, Plummer, and Boothby.

Dietary advice was given, and rest during the day was insisted upon. Psychotherapy was administered, and Social Service assistance was utilized to improve the home environment and minimize stress and strain. Hospitalization on one or more occasions during the ante-partum course was considered necessary in 11 of the 13 cases reaching viability or term. The average duration of such an admission was nineteen days. These patients were also admitted for an average of ten days before their confinement.

Adequate ante-partum care played an important part in carrying these patients to term, since the weight, pulse rate, blood pressure, and the basal metabolic rate could be observed at regular intervals. Close cooperation with the medical and surgical services was considered important in the care of the patients.

Cardiac disease on a valvular basis, irrespective of the thyroid disease, was present in 2 cases. The average pulse rate during the ante-partum course was 104 per minute, and after iodine therapy had been given for about ten days, there was a slight decrease in the rate to 96 per minute.

The average weight at the beginning of pregnancy was 58 kilograms (127.6 pounds), which is approximately the same as the average for the clinic according to Pastore. The average weight gain during pregnancy was 14 kilograms (30.8 pounds), or 24 per cent; which is the same as the clinic figure. However when the 13 cases reaching viability or term are studied, it is observed that 6 patients, or 46.1 per cent, failed to gain weight properly; in fact, two patients lost weight. This failure to gain weight in a normal manner was attributed to the hyperthyroidism.

Toxemia of pregnancy was observed in 10 cases, or 76.9 per cent of the cases reaching viability or term; the clinic incidence of toxemia is 6.7 per cent. The classification of the American Committee on Maternal Health was used, and the types of toxemia are given in Table II.

TABLE II. THE TYPES OF TOXEMIA OF PREGNANCY IN HYPERTHYROIDISM

	NUMBER OF CASES
Pre-eclampsia, severe	2
Pre-eclampsia, mild	2
Hypertensive disease	2
Renal disease	4
Total	10

From the average basal metabolic rate as shown in Fig. 1, it will be seen that for the first, second, and third trimesters of pregnancy, the values are plus 26 per cent, plus 36 per cent, and plus 35 per cent, respectively. There was a moderate reduction in the rate to plus 26 per cent following iodine therapy. A probable basal metabolic rate curve for normal pregnancy is also shown in Fig. 1, and was obtained as shown in Fig. 3. This curve shows a normal rise in the metabolic rate to plus 12 to 16 per cent at term. On this basis one could expect a rise in the hyperthyroid patients to plus 45 per cent, but this did not take place. This suggests that the thyrotoxicosis may even be ameliorated by the pregnancy. On the tenth to twelfth post-partum day, the rate is still elevated as before delivery, whereas in normal patients a return to normal readings is observed. Since delivery has removed the products of conception, and consequently the active protoplasmic mass of the fetus, the elevated rate post-partum is evidently due to thyroid hyperplasia. Is it not hyperplasia of the thyroid gland concomitant with pregnancy, rather than protoplasmic mass, that causes the increased metabolic rate in normal patients?

TABLE III. THE TYPES OF DELIVERY OR TERMINATION OF PREGNANCY

	NUMBER OF CASES
Spontaneous	10
Operative	3
Abortion { Spontaneous	1
{ Induced	4
Total	18

minute, the blood pressure was 170 systolic and 90 diastolic (millimeters of mercury), and there was no albumin in the urine. There was a palpable adenomatous goiter, and the basal metabolic rate was plus 45 per cent. A clinical diagnosis of adenomatous goiter, and toxemia of pregnancy was made and the patient was admitted to the hospital where she remained until delivery.

Observations of the pulse rate, weight, blood pressure, and the basal metabolic rate were made as shown in Fig. 2. Syrup of hydriotic acid was given, the patient was confined to her bed, and a routine low protein diet was ordered because of the toxemia of pregnancy. This diet has 275 Gm. of carbohydrate, and was changed to a high carbohydrate diet when the hyperthyroidism became more evident. There was gradual improvement, the weight increased slightly, and the blood pressure became lower, and the basal metabolic rate decreased to plus 29 per cent. The fluid intake averaged 2,500 c.c. daily, with a urinary output of 1,200 to 1,500 c.c. daily. The fundi oculi showed suggestive signs of early sclerosis. The blood chemical studies before delivery have been summarized in Table V. The values are essentially normal except for the lowered carbon-dioxide combining power.

TABLE V. THE AVERAGE BLOOD CHEMICAL VALUES (AVERAGE OF 2 TESTS) IN THE CASE REPORTED

Nonprotein nitrogen	34.7 mg.
Uric acid	3.1 mg.
Chlorides	493.0 mg.
Sugar	88.0 mg.
Carbon dioxide	39.6 volumes per cent
Urea clearance	157.0% in 2 hours
Phenolsulphonethylthalein	96.0% in 2 hours

After a stay of forty-two days in the hospital, and since the baby was viable, and because the uterus had become irritable, a medical induction of labor consisting of castor oil, quinine, an enema, and eight doses of pituitrin intranasally, was given. It was successful, and after a short labor of ten hours, delivery was accomplished spontaneously. No analgesia was used, and nitrous oxide and oxygen was given for several minutes for the actual delivery. The infant weighed 2,900 Gm. (6 pounds, 7 ounces), and was in good condition. There was no thyroid crisis.

On the tenth postpartum day the basal metabolic rate was plus 21 per cent, and six months later it was plus 34 per cent. Thyroidectomy was performed in the eighth month post partum. Prior to the operation, as shown in Fig. 2, the patient failed to gain weight, and the blood pressure was still elevated, although the blood pressure was nearer normal. After the operation immediate improvement was observed, the patient gained weight, the pulse rate became normal as did the basal metabolic rate and blood pressure.

#### DISCUSSION

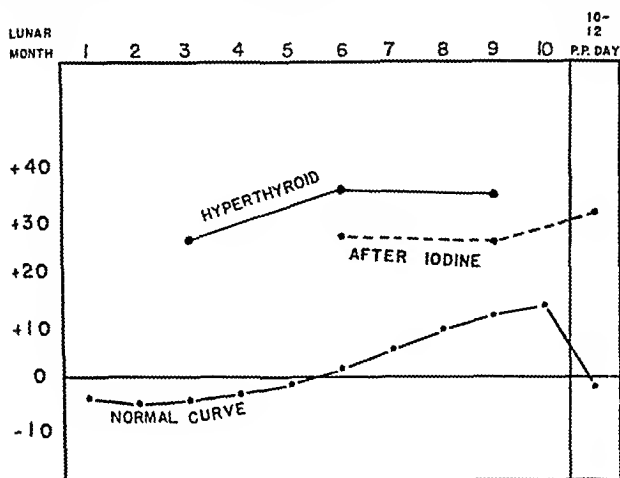
The data presented above are from a study of only 18 cases, nevertheless a period of seven years is covered, during which time 23,439 patients were delivered. These cases illustrate the policy of the Woman's Clinic with regard to hyperthyroidism and pregnancy. The incidence of this complication of pregnancy was only 0.076 per cent, which is in agreement with the incidence of Wallace in Brooklyn, as shown in

TABLE VI. THE INCIDENCE OF HYPERTHYROIDISM AND PREGNANCY

			INCIDENCE
Javert	New York	18 cases in 23,439	0.076%
Wallace	Brooklyn	9 cases in 11,571	0.077%
Portis and Roth	Chicago	14 cases in 1,000	1.4%
Yoakum	Detroit	(Quoted by Wallace)	3.7%
Markoe	New York	8 cases in 100,000	0.008%

Thyroidectomy was not performed during pregnancy, even though 4 patients had an adenomatous type of goiter, although operation was advised but refused in one such case. However in the first post-partum year, operation was advised in all of the 5 severe cases, and was permitted in 3 of the patients.

Therapeutic abortion was performed in 4 patients, or 22.2 per cent, which is a high incidence. However 3 of these were private patients.



### BASAL METABOLIC RATE IN PREGNANCY

### WITH HYPERTHYROIDISM - 18. CASES

Fig. 1.

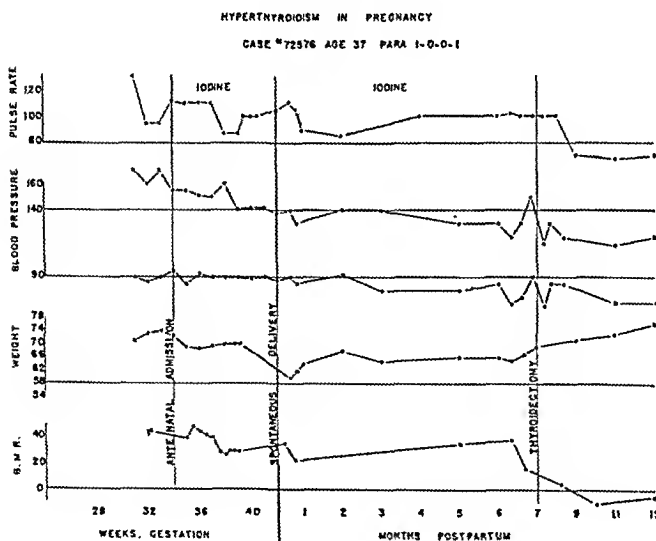


Fig. 2.

### CASE REPORT

This case illustrates the clinical management and treatment of a patient with hyperthyroidism and pregnancy. The patient was a 37-year-old woman, white, para 1-0-0-1, with a normal past obstetric history. The thyroid symptoms antedated the present pregnancy by only several months. She registered in the clinic in the thirty-second week of gestation, at which time the pulse rate was elevated to 100 per

per cent for the last trimester of pregnancy. A probable basal metabolic curve for normal pregnancy is also shown in Fig. 3, based on the data of the investigators named, as well as from current knowledge of the test; and it is generally believed that an increase to plus 12 to 16 per cent occurs at term. The lower rate is probably due to better apparatus and technical skill, as well as the education of the patients after several tests. DuBois states that the present normal standard, which is now arbitrarily placed at zero, is probably nearer minus 5 per cent for a patient having had several tests (as in the several trimesters of pregnancy).

The increase in the metabolic rate during gestation has been attributed by Sandiford and Wheeler, Hanna, and others to active protoplasmic mass of the fetus. Hanna adds that thyroid hyperplasia associated with pregnancy may also be a factor, which is tenable since visible hypertrophy of the gland occurs in 41 per cent of pregnant women according to Davis, and palpable enlargement up to 90 per cent according to Hinton. In the hyperthyroid patients in this report, the

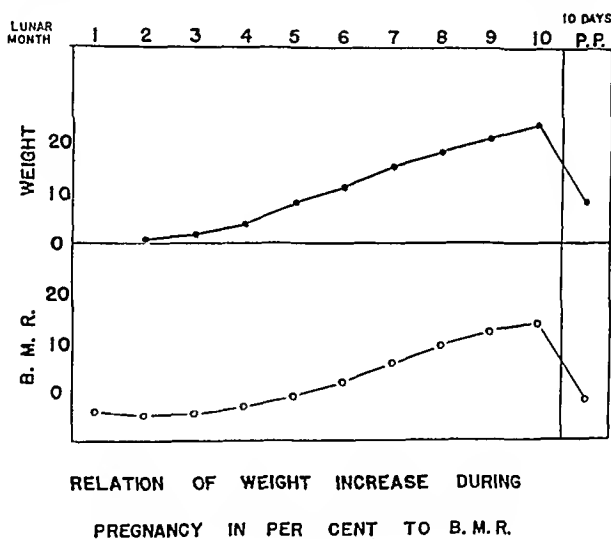


Fig. 4.

metabolic rate remained elevated after delivery had removed the products of conception, which may be interpreted as indicating that thyroid hyperplasia and not active protoplasmic mass affects the basal metabolic rate. It is to be remembered that part of the weight gain in pregnancy is due to hydremia and amniotic fluid.

The monthly average weight gain in pregnancy has been studied in 2,500 normal patients by Pastore. If the increase is expressed in percentage, a curve is obtained as shown in Fig. 4, an increase to 24 per cent occurring at term. In comparing this weight curve with the probable basal metabolic rate curve, it is evident that they parallel each other, with a decrease in both after delivery. This supports the theory of active protoplasmic mass as the cause of the normal increase in the basal metabolic rate in pregnancy. However as pointed out above, thyroid enlargement occurs in 40 to 90 per cent of the patients in preg-

Table VI. This table also shows a higher incidence in the cities in the goiter district. The very low incidence of Markoe was recorded in the days before the basal metabolism test was in general use.

Iodine was used without hesitation for long periods of time even in the patients with nodular goiter without evidence of harmful effect. Davis has had similar experience and began the use of iodine in pregnancy in 1926, following Marine and Kimball's reports (1921) on the prophylactic use of iodine in adolescent goiter. Mussey cautions against the use of iodine in adenomatous goiter, but advises it in diffuse exophthalmic goiter. Graham has shown iodine to be beneficial in both types of hyperthyroidism.

The benefits of iodine extend also to the fetus. Else and Davis state that congenital goiter may develop unless iodine is administered. Debrecca states that iodine is compulsory during pregnancy in Berne, Switzerland. Fenger has found iodine in the thyroid gland in the fetal calf as early as the third month of pregnancy.

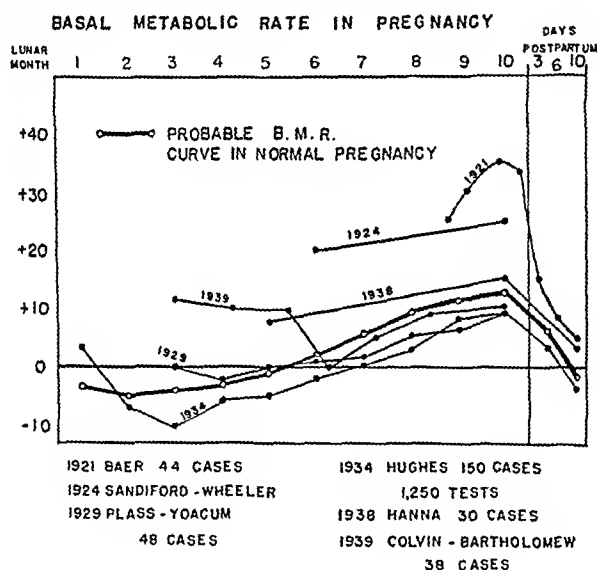


Fig. 3.

The incidence of toxemia of pregnancy was 76.9 per cent, which is a marked increase over the elinie figure of only 6.7 per cent. Are we to again give credence to the older views that toxemia and thyrotoxicosis are related to each other? Colvin and Bartholomew found an incidence of toxemia of pregnancy in 38 per cent of patients having an elevated basal metabolic rate. Conversely, Stander and Peekham, in an earlier study, showed an increased metabolic rate in patients with toxemia. Wiegand has shown an increased function of the thyroid gland in eclampsia, while Anselmino and Hoffmann, Soule, and others have demonstrated an increased amount of a thyroxinlike substance in pregnancy.

The basal metabolic rate in pregnancy was first studied by Magnus Levy in 1887, and since then by many other investigators, including Baer, Sandiford and Wheeler, Hughes, Plass and Yoakam, Hanna, Colvin and Bartholomew. The data obtained by these workers are shown in Fig. 3, and the earlier tests show values up to plus 25 to 35



tients were admitted to the hospital more than once for an average stay of nineteen days. These patients were likewise admitted for ten days before delivery.

Analgesia during labor should have been used more frequently. The use of nitrous oxide anesthesia is also open to criticism, not only because of the hyperthyroidism, but also because of the associated toxemia of pregnancy. Lahey advises cyclopropane for operation in these patients, since their oxygen requirement is 2 to 3 times greater than in normal patients. However no ill effects were observed following nitrous oxide, oxygen and ether inhalation, probably because the duration of the anesthetic was short, since most of the patients were multiparas. Local anesthesia for the episiotomy, preceded by adequate analgesia, should be very satisfactory. It is being used more and more in patients with toxemia, diabetes, tuberculosis, and cardiac disease.

The association of hyperthyroidism and sterility has been repeatedly mentioned in the literature, including the recent review of the thyroid gland and pregnancy by Mussey. He quotes Carey, Randall, Titus, Bloss, and others, as giving thyroid extract to sterility patients to improve their fertility. If the presumption is correct, hyperthyroid patients should be unusually fertile, which is certainly not the case. Mussey reports only 42 pregnancies in 7,228 patients with hyperthyroidism, an incidence of 0.6 per cent. Conversely, hyperthyroidism and pregnancy has a lower incidence of 0.07 per cent in the author's series. Since this study was made, subsequent pregnancy has been reported in only 1 case, and only one patient could date the onset of hyperthyroid symptoms to a previous pregnancy. However the role of contraception in these patients must be considered as a possible reason for their sterility.

Follow-up studies for a year or more in the majority of the cases revealed no evidence of aggravation of the hyperthyroidism by the pregnancy in the mild or moderately severe cases. This was also true of the 5 severe cases, three were operated upon in the first post-partum year, although one of the severe cases was regarded as slightly worse because of the pregnancy.

#### SUMMARY AND CONCLUSIONS

1. There were 18 cases of hyperthyroidism in 23,439 pregnant women, an incidence of only 0.076 per cent, which is a low figure in a seacoast city as compared with higher incidences in cities in the goiter district.

2. With proper treatment, patients suffering from hyperthyroidism may safely go through a pregnancy, and sometimes even be benefited thereby. Hospitalization for evaluation and stabilization may be necessary several times during the ante-partum course.

3. Iodine therapy in our experience is without danger even over long periods of time both during and after pregnancy. There is some question regarding ill effects of iodine in adenomatous goiter, while its use in diffuse goiter is generally accepted.

4. Therapeutic abortion is rarely indicated, although it was performed in 22 per cent of the cases, most of which were private patients.

nancy, and Abbott has demonstrated hyperplasia in the thyroid glands of pregnant cows on histologic examination. One may conclude that the normal rise in the basal metabolic rate is due to thyroid hyperplasia concomitant with pregnancy. In the hyperthyroid patients of this study, the rate was essentially the same in the second and third trimesters of pregnancy (plus 36 per cent and plus 35 per cent) as it was post partum (plus 33 per cent), showing that hyperactivity of the thyroid gland and not the protoplasmic mass of pregnancy was responsible. On the other hand, it may be said that this shows aggravation of the hyperthyroidism by the pregnancy, which was not substantiated by the clinical course of the patients. In fact, the failure of the metabolic rate in the third trimester to exceed that of the second trimester indicates that pregnancy was exerting a beneficial effect. Portis and Roth state that in certain cases the thyroid condition may even be ameliorated, which view is supported by the investigations of Bodansky and Duff on rats. They showed that pregnant rats tolerated larger doses of thyroid extract than did the nonpregnant animals.

Therapeutic abortion was performed in 22.2 per cent of the patients, which seems high, but 3 of these were private patients. If we study the 171 abortions done for therapeutic reasons in the Woman's Clinic in the past seven years, it is learned that 4 or 2.34 per cent were performed because of hyperthyroidism. Wallace and Bothe state that it is never indicated, and Means says that the thyrotoxicosis and not the pregnancy should be interrupted. Hinton makes an exception if cardiac changes are marked, or if the hyperthyroidism is of the fulminating type. Fahrni states that interruption is more dangerous than a well-performed thyroidectomy, especially in the third to the fifth month of gestation. It is to be remembered that abortion does not cure the thyroid disease, and carries an added risk of infection, and even of a thyroid crisis.

Thyroidectomy was not performed in the author's cases, although it was advised in 1 case. This operation during pregnancy has its advocates in Mussey, Polowe, Portis and Roth, Means, Frazier, Fahrni and others. Mussey favors operation in adenomatous goiter in preference to iodine therapy. On the other hand, Brams says that 90 per cent of pregnant women can be carried to term without thyroidectomy, and Bothe agrees that it is rarely necessary. Thyroidectomy during pregnancy is objectionable on the grounds that the gland has become hyperplastic and vascular, making it difficult to judge how much of the gland to remove. A second operation may be necessary, or myxedema may develop. Furthermore the effects of the operation on the unborn child are uncertain. In normal pregnant dogs, according to Stander, thyroidectomy results in large thyroid glands in the puppies. Williamson has cautioned the profession regarding this possibility in human beings, and advises thyroid extract, iodine, sedation, and rest if a thyroidectomized woman becomes pregnant. This advice probably also applies to those operated upon during pregnancy.

Hospitalization during the ante-partum course was considered important in the majority of patients carried to term. Many of the pa-

# ENDOMETRIOSIS\*

## A STUDY OF 260 PRIVATE HOSPITAL CASES

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TOO often perhaps, reports are made concerning the diagnosis and treatment of various conditions based upon the records of large clinics, which are administered by experts. These results should be much better than the average. One wonders if a cross section of the care of these conditions by the average surgeon, working in an average private hospital, might not be very instructive, and although perhaps renewing our humility to some degree by the less excellent mortality and morbidity records, give a more exact estimate of the treatment accorded patients of the higher social levels.

The subject of endometriosis is excellently adapted to a review of the records of private hospitals, because it has been the observation of numerous investigators that this condition is more prevalent among women in the middle or upper strata of society.

In reviewing the voluminous literature on endometriosis one is impressed not only by the large percentage of failures to make a pre-operative diagnosis, but by the lack of standardization in the treatment of this condition. Also in discussing the problem with our colleagues, particularly general practitioners and general surgeons, the conclusion is forced upon us that there is too often a failure to make a diagnosis with the abdomen open, and consequently a failure to apply proper or adequate treatment.

It was therefore with these thoughts in mind that a study of 260 cases, taken from the record rooms of two private Los Angeles hospitals, was undertaken.

### STATISTICAL SUMMARY

There are 260 cases of proved endometriosis in this series which comprise all the known cases of endometriosis at two private Los Angeles hospitals from the period of May, 1930, to April, 1939. All of these women were operated upon and the diagnosis established or substantiated by pathologic examination of the removed tissues. Patients diagnosed clinically and not operated upon were not included. Cases diagnosed by the surgeon at the operating table, not substantiated by examination of removed tissue by the pathologist, were rejected. It is of interest that, in assembling the cases for this series, many cases of hemorrhagic ovarian cysts, diagnosed as endometriosis by the surgeon, were discarded, due to lack of pathologic confirmation. However, it was noted by the writers that in nearly every instance where dense adhesions were stated to be present, the pathologist was able to confirm a diagnosis of endometriosis.

These 260 women were operated upon by 63 surgeons. There were in this group of operators many general surgeons, a few gynecologists, and several general practitioners.

\*Presented at a meeting of the Pacific Coast Society of Obstetrics and Gynecology, November 3, 1939.

5. Thyroidectomy was not performed during pregnancy. The optimum time for this operation is believed to be in the first post-partum year in the cases where it is indicated, so that the effects of pregnancy on the gland are no longer present. However thyroidectomy may be performed regardless of the pregnancy in the individual case, as shown by reports in the literature.

6. The high incidence of toxemia of pregnancy (76 per cent) in the present study seems to be of significance, and raises the question of a common factor in toxemia and thyrotoxicosis.

7. The increase in the basal metabolic rate in normal pregnancy may be entirely due to thyroid hyperplasia concomitant with the pregnancy, rather than to the active protoplasmic mass of the fetus. In the 18 cases, the rate was virtually the same in the second and third trimesters of pregnancy, and immediately post partum when the products of conception had been delivered; normally the basal metabolic rate returns to nonpregnant levels.

8. A probable basal metabolic rate curve for normal pregnancy, based on the current knowledge of the test, is presented.

9. Pregnancy may have an ameliorating effect on the hyperthyroidism. Only one case was thought to have been aggravated by the gestation.

10. Nitrous oxide, oxygen, and ether anesthesia was used for delivery which was usually spontaneous and of short duration, since most of the patients were multiparas. Local anesthesia is preferred.

11. A case report showing the management and clinical course as practiced in the Woman's Clinic of the New York Hospital is presented.

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TABLE III. AGE INCIDENCE\*

AGE IN YEARS	DISTRIBUTION ACCORDING TO TYPE					
	INTERNAL		EXTERNAL		COMBINED	
	NO. CASES	PER CENT	NO. CASES	PER CENT	NO. CASES	PER CENT
15-19	0	0.0	0	0.0	0	0.0
20-24	0	0.0	2	2.1	2	5.5
25-29	7	5.4	17	17.9	4	11.1
30-34	13	10.0	33	34.8	5	13.9
35-39	25	19.3	22	23.2	9	25.0
40-44	35	27.1	11	11.6	8	22.2
45-49	31	24.0	8	8.4	7	19.4
50-54	14	10.9	1	1.0	1	2.8
55-59	3	2.3	1	1.0	0	0.0
60-64	1	0.8	0	0.0	0	0.0
65-69	0	0.0	0	0.0	0	0.0
Total	129	100.0	95	100.0	36	100.0

\*Illustrating that the external or pelvic type of endometriosis is operated at an earlier age than the uterine type.

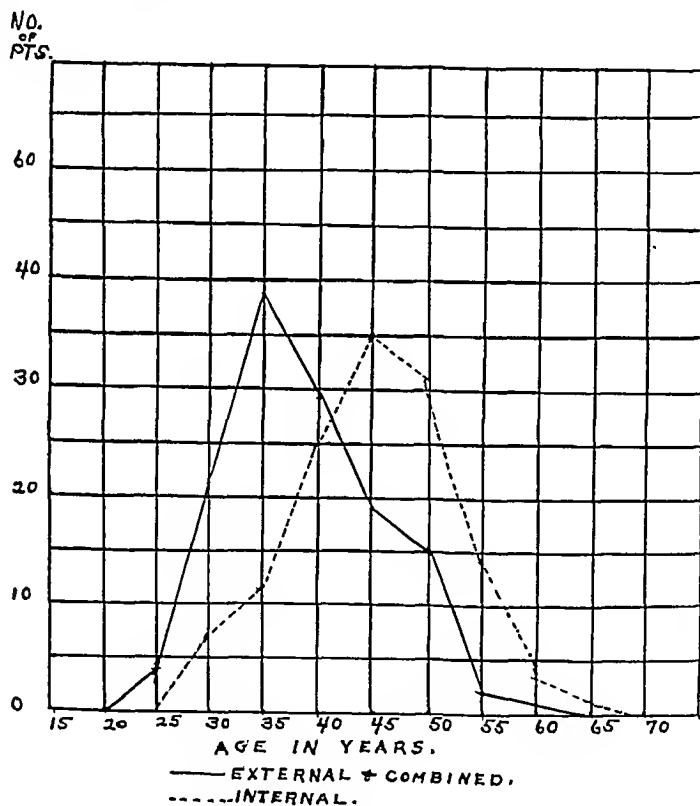


Chart 1.—Graph showing age incidence.

external type of endometriosis. At first glance this would seem to show that adenomyoma develops later in life than do the other types of endometriosis. However, it may well be that this apparent fact is false. It is possible that each type develops at correspondingly the same ages, but that adenomyoma is more slow in developing symptoms requiring surgery.

The external type of endometriosis in our series reaches its peak of incidence in the age group of 30 to 34 years; 75.7 per cent of all our cases

TABLE I. INCIDENCE

Number of cases in series	260
Number of gynecologic laparotomies performed during this period	15,975
Per cent of proved endometriosis cases to all gynecologic laparotomies done	1.62%

A percentage of 1.62 is extremely low, and we believe does not represent a true incidence of endometriosis in this group of 15,975 gynecologic laparotomies. Most authors have estimated the incidence of endometriosis to be about one in ten. Two reasons for this apparently false percentage in our series present themselves. First, we have accepted only laboratory proved cases and have undoubtedly discarded many cases of true endometriosis. Second, our 15,975 laparotomies represent the work of numerous operators and undoubtedly many cases of endometriosis have failed of recognition.

## CLASSIFICATION OF TYPES

For purpose of simplicity in the presentation of our statistics we have divided our cases into 3 types, as follows: (1) Internal or uterine type: Cases involving the uterus alone, the so-called adenomyoma. (2) External or pelvic type: Cases involving structures other than the uterus. (3) Combined type: Cases involving both uterus and pelvic structures.

We feel that the purposes of this paper can be better served by a simple division of cases such as the above, rather than a more complicated classification, as that of Newmann. In tabulating our statistics we have clearly distinguished between the internal or uterine type of endometriosis, the so-called adenomyoma, and the external or pelvic type. The treatment in these two major groups must be quite different. The external and the combined group (in which the uterus is involved in addition to other structures) tend to fall into one treatment group.

TABLE II. CLASSIFICATION OF TYPES

TYPE	NUMBER	PER CENT
Internal	129	49.6
External	95	36.5
Combined	36	13.9
Total	260	100.0

## AGE INCIDENCE

Table III shows that the greatest incidence in our series was between the ages of 30 and 50 years, with the peak reached in the decade between 35 and 45 years. The fact that it does occur in the third decade and as late as the seventh must always be remembered. The youngest patient in our series was 21 years old and the oldest 63. Counsellor has reported a patient of 73 years of age.<sup>1</sup> The age incidence in our group corresponds closely with that of previously reported groups.

It is evident from a study of Table III and Fig. 1 that in our series adenomyoma was operated upon in a later age group than was the

There was a high incidence of ovarian pathology other than that of endometriosis of the ovaries, there being 66 such cases or 25.0 per cent. The high incidence of menstrual disturbances, as will be shown later, may be due to this. Dysmenorrhea may be caused by any type of ovarian lesion, and it is possible that some of these cases of dysmenorrhea were due to associated ovarian pathology rather than to the endometriosis itself. Table V lists the number and types of pathologic lesions found associated with our cases of endometriosis.

TABLE V. ASSOCIATED PATHOLOGY

	IN- TERNAL	EX- TERNAL	COM- BINED	TOTAL	*PER CENT
Fibroid uterus	52	34	22	108	41.5
Ovarian pathology					
Simple follicular cysts	24	8	5	37	14.2
Lutein cysts	7	1	1	9	3.2
Inflammatory cysts	4	3	0	7	2.7
Multilocular cystadenoma	1	1	1	3	1.1
Hemorrhagic cysts (not chocolate)	1	1	0	2	0.8
Carcinoma ovary	0	2	0	2	0.8
Papillary cystadenoma	0	1	0	1	0.38
Dermoid cysts	0	1	0	1	0.38
Pseudomucinous cysts	0	0	1	1	0.38
Fibromas ovary	0	1	0	1	0.38
Fibrosis ovary	0	0	1	1	0.38
Granulosa cell tumor	1	0	0	1	0.38
Chronic pelvic inflammatory disease	26	16	3	45	17.3
Endometrial hyperplasia	13	10	5	28	10.7
Chronic appendicitis	9	11	2	22	8.4
Endometrial polyp	12	3	6	21	8.0
Fibrosis uteri	10	5	2	17	6.5
Cervical polyp	2	0	1	3	1.1
Pregnancy, intrauterine	2	0	0	2	0.8
Carcinoma body uterus	2	0	0	2	0.8
Carcinoma cervix	1	0	0	1	0.38
Carcinoma bladder	1	0	0	1	0.38
Uterus bicornis unicollis	0	1	0	1	0.38

\*Percentage computed on basis of number of cases. Therefore does not total 100 per cent because of multiple lesions.

#### SYMPTOMATOLOGY

A cardinal symptom of endometriosis is some disturbance of the menses. This may take the form of dysmenorrhea, menorrhagia, polymenorrhea, metrorrhagia, or frank uterine hemorrhage.

#### DYSMENORRHEA

Dysmenorrhea is a predominant complaint in our series. It was noted in 113 instances, or 43.4 per cent of the total number of cases. The distribution was as shown in Table VII.

It is apparent that dysmenorrhea was a more constant symptom in the general pelvic than in the uterine type of endometriosis in this series.

of this type were between the ages of 25 and 40 years. This fact presents a difficult problem in treatment. Most authors agree that ablation of all ovarian tissue after the age of 40 years in general pelvic endometriosis is indicated, but if three-fourths of the cases occur at earlier ages it would seem to be justifiable to operate radically at even an earlier age.

#### ORGANS INVOLVED

The anatomic distribution of lesions in this series follows closely that described by previous authors. Inasmuch as our series includes adenomyomas of the uterus, that organ was involved the greatest number of times, there being 162 such instances. The ovary showed the next greatest involvement, 84 lesions. There were 361 organs involved, many patients having double or multiple lesions.

TABLE IV. INVOLVEMENT OF ORGANS

ORGAN	NUMBER	PER CENT OF TOTAL ORGANS INVOLVED
Uterus	162	44.8
One ovary alone 53 }	84	23.2
Both ovaries 31 }		
Pelvic peritoneum	51	14.2
Rectovaginal septum	16	4.4
Bladder	11	3.0
Sigmoid	10	2.8
Fallopian tubes	6	1.6
Small intestine	5	1.4
Round ligament	4	1.1
Uterosacral ligament	3	0.83
Abdominal wall, p.o. scar	3	0.83
Appendix	2	0.56
Umbilicus	2	0.56
Infundibulopelvic ligament	1	0.28
Stump of cervix	1	0.28

#### ASSOCIATED PELVIC DISEASE

The relationship between endometriosis, fibromyomas, and endometrial hyperplasia has been described by Witherspoon and others.<sup>2</sup> Our series shows a high incidence of these lesions. Fibromyoma of the uterus occurred 108 times or in 41.5 per cent of our cases. In addition there were 17 instances where the pathologist diagnosed fibrosis of the uterus. These two lesions therefore total 125, or 48.0 per cent. The fact that less than half of these cases were of the internal or uterine type, as may be seen in Table V, is interesting, and again suggests the possibility of a common etiologic factor in fibromyoma and endometriosis.

Endometrial hyperplasia was diagnosed 28 times or in 10.7 per cent; while endometrial polyps were noted 21 times or in 8.0 per cent. These two lesions total 49, or 18.7 per cent; again an incidence considerably higher than could be found in any unclassified group of pelvic cases. It is quite likely that there were many other cases in our series in which there was an associated hyperplasia of the endometrium, particularly in the external type, because obviously no pathologic study was made of the uterus in many of these cases.



## POSITION OF THE UTERUS

Position of the uterus could not be satisfactorily evaluated in this series. A retroposition of the uterus is believed to be an etiologic factor in endometriosis, other series showing a high incidence of retrodisplacement. In this series, in 127 instances, or 48.8 per cent, the position of the uterus was not stated on the record of the physical examination. Inasmuch as these were all pelvic cases (with the exception of the 3 cases of involvement of abdominal wall in postoperative scars) and a pelvic examination was done in every case, this omission seems to us to be a serious error and possibly explains some of the diagnostic pitfalls. Of the 133 stated cases 70, or 52.6 per cent, showed some type of retroposition.

## PREVIOUS ABDOMINAL SURGERY

In compiling our statistics of previous surgical procedures we have considered only abdominal operations, because of the uncertainty of the records concerning vaginal procedures. Many of the patients stated in the history that they had had some type of vaginal operation, but were not sure as to whether it was a curettage, cauterization, or repair. While the number of patients who had had curettage of the uterus would be of interest, we felt that the figures would not be reliable, and therefore they were omitted. In tabulating abdominal surgery, we have distinguished between those cases in which the uterus, tubes, or ovaries were cut into (with the possibility of transplanting tissue of the endometrium, the endosalpinx or the ovarian cortex), and those in which other procedures were done. Ninety-six patients, or 36.9 per cent, had had a previous laparotomy.

TABLE IX. PREVIOUS ABDOMINAL SURGERY

TYPE	TOTAL NUMBER OF PATIENTS	PATIENTS WITH PRE- VIOUS LAP- AROTOMIES	PER CENT	PATIENTS WITH UTER- US, TUBES, OR OVARIES CUT INTO	PER CENT
Internal	129	53	41.0	34	26.3
External	95	29	30.4	15	15.7
Combined	36	14	38.6	6	16.6
Total	260	96	36.9	55	21.1

It would, from a study of this table, be difficult to draw any conclusion which would appreciably add weight to the theory of surgical distribution of endometrial tissue as an etiologic factor in the development of endometriosis. Almost as many in our series had other types of abdominal operations prior to developing endometriosis as had surgery which might be a cause of it.

## TREATMENT EMPLOYED

The treatment of adenomyoma is simply a destruction of the lesion itself. This is accomplished usually by hysterectomy; less frequently by radiation. The cure of external endometriosis is not so easily accomplished, nor are surgeons so uniformly in accord as to the surgical indications.

TABLE VI. SYMPTOMATOLOGY

COMPLAINT	INTERNAL	EXTERNAL	COMBINED	TOTAL
Menorrhagia	66	18	19	103
Metrorrhagia	23	17	12	52
Polymenorrhea	21	1	1	23
Uterine hemorrhage	3	1	0	4
Dysmenorrhea	40	54	19	113
Lower abdominal pain	34	44	12	90
Backache	24	9	2	35
Abdominal tumor (noted by patient)	10	11	5	26
Vaginal discharge	9	9	1	19
Bladder symptoms	7	4	2	13
Rectal pain	2	3	2	7
Postmenopausal bleeding	4	0	1	5
Gastrointestinal upsets	0	1	4	5
Dyspareunia	0	3	1	4

TABLE VII. DYSMENORRHEA

TYPE	TOTAL NUMBER OF PATIENTS	PATIENTS WITH DYSMENORRHEA	*PER CENT
Internal	129	40	31.0
External	95	54	56.7
Combined	36	19	52.7
Total	260	113	43.4

\*Percentage computed according to each type. Therefore does not total 100 per cent.

## EXCESSIVE UTERINE BLEEDING

One hundred and twenty-four patients, or 47.7 per cent, complained of excessive uterine bleeding, taking the form of menorrhagia, metrorrhagia, polymenorrhea, or any combination of these. These cases were distributed as shown in Table VIII.

TABLE VIII. EXCESSIVE BLEEDING

TYPE	TOTAL NUMBER OF PATIENTS	PATIENTS WITH EXCESSIVE BLEEDING	PER CENT
Internal	129	67	51.9
External	95	37	38.9
Combined	36	20	55.5
Total	260	124	47.7

As would be expected, in our series excessive uterine bleeding is a more frequent finding in the uterine type of endometriosis.

## OTHER SYMPTOMS

The symptoms elicited in our clinical histories have been shown in Table VI. Lower abdominal pain follows menstrual abnormalities in frequency of occurrence. Bladder and rectal pain were not found to occur as frequently as has been stressed by other writers. The occurrence of 5 cases of postmenopausal bleeding, in each of which there was adenomyoma of the uterus, is interesting and important. Endometriosis has not been stated to be a cause of postmenopausal bleeding.

"chronic inflammation of the terminal ileum," and in the other, "a scar at Meckel's diverticulum." Neither patient complained of nausea or vomiting, or exhibited any signs of intestinal obstruction. In the third case, there was a mass of endometriosis attached to the sigmoid. The operator stated that he could not easily separate this, and although both ovaries were removed, he did not feel that the endometrial mass should be allowed to remain. Consequently this mass, including a segment of the sigmoid, was removed and an anastomosis of large bowel done.

All of the above three patients survived the increased hazard of an intestinal resection, although the postoperative course of the patient, having the large bowel resection, was prolonged and stormy. It appears in reviewing these cases that bowel resection was not justified. Bilateral ovarian ablation would have effected a cure in each case.

#### DIAGNOSIS

Table XII presents a record of preoperative diagnosis, and of the diagnoses made with the abdomen open. It will be seen that there were only 6.9 per cent of preoperative diagnoses made. While this is admittedly small, we feel under no necessity to apologize. We believe that if similar statistical studies were made elsewhere they would be much the same.

We can find less excuse, however, for the fact that in only 106 cases, or 40.7 per cent, was the diagnosis made with the abdomen open. It seems that in spite of a voluminous literature on the subject, our surgeons are still not endometriosis conscious.

We feel that the statistics contained particularly in Tables XI and XII furnish ample justification for our study of endometriosis.

TABLE XII. DIAGNOSIS

Cases in series	260	-
Number diagnosed preoperatively	12	
Number suspected preoperatively	6	
Number either diagnosed or suspected preoperatively	18	6.9%
Number not suspected nor diagnosed preoperatively	242	93.1%
Number diagnosed at surgical table	89	
Number suspected at surgical table	17	
Number either diagnosed or suspected at surgical table	106	40.7%
Number not diagnosed nor suspected at surgical table	154	59.3%

#### MORTALITY

There were 2 deaths in this series, a rate of 0.77 per cent. Considering the gravity of some of the cases, we regard this rate as low.

One of these deaths occurred on the third postoperative day from paralytic ileus. The patient was operated upon for intestinal obstruction and massive endometriosis of the pelvis, with numerous dense adhesions in which loops of intestine were involved, was found.

The other death occurred on the thirteenth postoperative day. The case was one of adenomyoma with a submucous fibroid. The postoperative course was febrile and death may have resulted from postoperative infection. No autopsy was done.

All patients in this series were operated upon; as previously stated, only cases with diagnoses confirmed by examination of removed tissues being included. The terms conservative and radical are used only in relationship to the treatment of the ovaries. The surgery is tabulated as radical only if both ovaries were completely removed, any other surgery being considered as conservative, no matter what else was done. However, ovarian transplants, where both ovaries were removed from the abdomen and transplanted into the abdominal wall, must be considered as radical surgery. We feel that we are justified in this tabulation because of the short life of the transplant, which is thought to be about two years at best. Ovarian transplants were done in 9 cases.

Table X shows the incidence of conservative and radical surgery according to the type of endometriosis.

TABLE X. TYPE SURGERY EMPLOYED

TYPE ENDOMETRIOSIS	NO. CASES	CON- SERVATIVE SURGERY	PER CENT	RADICAL SURGERY	PER CENT
Internal	129	106	82.1	23	17.9
External	95	54	56.8	41	43.2
Combined	36	15	41.6	21	58.4
Total	260	175	67.3	85	32.7

We have made a study of the type of surgery employed in the various age groups of all those cases demonstrating external endometriosis.

TABLE XI. SURGERY IN VARIOUS AGE GROUPS

AGE	EXTERNAL ENDOMETRIOSIS		COMBINED ENDOMETRIOSIS		TOTAL			
	CONSERV- ATIVE	RADICAL	CONSERV- ATIVE	RADICAL	CONSERV- ATIVE	PER CENT	RADI- CAL	PER CENT
19-24	2	0	1	1	3	75.0	1	25.0
25-29	13	4	1	3	14	66.6	7	33.3
30-34	22	11	3	2	25	65.8	13	34.2
35-39	9	13	3	6	12	38.7	19	61.3
40-44	4	7	3	5	7	36.8	12	63.2
45-49	4	4	3	4	7	46.7	8	53.3
50-54	0	1	1	0	1	50.0	1	50.0
55-59	0	1	0	0	0	0.0	1	100.0
60-64	0	0	0	0	0	0.0	0	0.0
Total	54	41	15	21	69	52.6	62	47.4

In studying Table XI one cannot avoid assuming a critical view. When we consider external endometriosis where the ovary is the primary factor in controlling the disease, we must conclude that our surgeons have been too conservative, particularly in the older age groups. Our patients showing this external type total 131. Of these, 69, or approximately 53 per cent, were treated conservatively. There were 37 patients operated upon after the age of 40 years, and of this group 15, or 40 per cent, were left with ovarian tissue.

Resection of bowel was performed 3 times, twice of the ileum and once of the sigmoid. In neither case of small bowel resection was the diagnosis of endometriosis made at operation. The lesion was called in one case

The above figures are, we believe, self-explanatory. While the results of radical surgery are apparently excellent, there are surprisingly few cases in the conservative group which are not largely relieved of symptoms. Of course only nine years have elapsed postoperatively for any patient in this series, and it may be that late sequelae may make the results less favorable, particularly in the conservative group.

It may be seen, however, that in our series the results of conservative treatment in pelvic endometriosis are distinctly of less benefit to the patient. When it is considered that of 37 patients past the age of 40, 40 per cent were treated conservatively; this must be considered either an error in recognizing the pathology, or an error in surgical judgment.

#### INTERESTING CASES

There were in our series two cases which are, we believe, sufficiently interesting to be presented in brief as follows.

**CASE 1.**—Mrs. D. A., white, female, aged 27 years, married, para 0, gravida 0. *Complaint:* Intermittent attacks of right lower abdominal pain. *Menstrual History:* Negative. No relationship between the pain of which she complains, and menstruation. *Surgery:* On March 31, 1939, an appendectomy and a suspension of the uterus were done. The uterus was described as normal, except as to position. Both tubes and ovaries were normal except that attached to the right tube was a small parovarian cyst. The appendix was bound down by numerous adhesions. *Pathologic Report:* Examination disclosed an unmistakable island of endometrial tissue within the meso-appendix. Repeated sections through the meso-appendix were cut and the same island was uniformly found in the same area. There was no possibility of this being an artifact, and it was believed that the island of endometrium had arisen from embryonic rest cells.

This case is apparently one of a single isolated, small endometrioma in the meso-appendix. No other areas of endometriosis were found in the pelvis or abdomen. We believe that this case may serve to illustrate the theory of embryonic cell rests.

**CASE 2.**—Mrs. C. C., white, female, aged 27 years, married, para i, gravida ii. *Previous Surgery:* Suspension of the uterus (modified Gilliam), and an appendectomy, 1929. Tubes and ovaries at that time were found to be normal, and there was no evidence of pelvic or abdominal endometriosis. *Complaint:* Pain and tenderness in right lower abdominal wall (at about the point of suture of the right round ligament in old Gilliam suspension of the uterus). Pain began shortly after operation and was worse at the time of menstruation. Patient could palpate a small lump in this area. *Diagnosis:* A diagnosis of endometrioma of right round ligament was made. *Surgery:* On Aug. 2, 1938, under spinal anesthesia, a hard, fibrous mass, cystic at certain points, and about the size of an acorn, was resected from the abdominal wall at the site of the old suspension stitch which approximated the right round ligament to the under surface of the right rectus fascia. Peritoneal cavity not explored. *Pathologic Report:* Confirmed diagnosis of endometrioma of right round ligament. *Follow-Up:* No symptoms had developed suggestive of pelvic endometriosis since surgery.

While we believe that no etiologic deductions are possible, this case suggests the probability of surgical transplant of tubal or uterine endometrial tissue.

#### SUMMARY

It will be repeatedly apparent in reviewing our statistics that this study was hampered by incomplete histories. Also accurate deductions as to results of treatment are impossible because we could contact less than 50 per cent of the cases in our series. However, we feel that certain facts brought out by our study warrant particular emphasis.

## FOLLOW-UP STUDY

A follow-up was attempted by means of a questionnaire addressed to all of our patients. Of the 258 sent out, a reply was received from 114 of them. The following study is based upon these replies.

*Sterility and Marital Status.*—Since the clinical history regarding the marital status, number of children, and sterility was inadequate we have relied entirely in this study upon replies to our questionnaires.

One hundred and two of these patients were married, or had been married. Twelve had never been married. Of the 102 married women 34, or 33.3 per cent, had had no pregnancies and may have been sterile.

TABLE XIII. MARITAL AND PARITY STUDY

	INTERNAL	EXTERNAL	COMBINED	TOTAL
Married	48	36	18	102
Not married	4	4	4	12
Married, no children	11	17	6	34

It will be noted in the figures above that the number of married women with pelvic endometriosis who had had no children is about double that of the married women with uterine endometriosis. The extent to which the reproductive function of the younger women treated by conservative surgery had been preserved, we are unable to estimate. Of the 114 women above responding to our questionnaire, only one had had a child since surgery. This was in the case of a woman, aged 32 years, married 7 years. At surgery both ovaries contained multiple small chocolate cysts, and there were endometrial transplants on the bladder. A partial bilateral oophorectomy was done, resecting the involved portions. The endometrial transplants elsewhere were excised where possible. Pregnancy followed twenty-seven months later. The patient is apparently well at present and has no symptoms of endometriosis.

## RESULTS OF SURGERY

The 114 patients whom we were able to contact were asked to evaluate the results of the operation. Their tabulated responses appear in Table XIV.

TABLE XIV

	IN- TERNAL	PER CENT	EX- TERNAL	PER CENT	COM- BINED	PER CENT
<i>Results of Radical Surgery</i>						
Relieved entirely	13	81.2	17	100.0	10	90.9
Relieved largely	3	18.8	0	0.0	1	9.1
Relieved slightly	0	0.0	0	0.0	0	0.0
Relieved not at all	0	0.0	0	0.0	0	0.0
<i>Results of Conservative Surgery</i>						
Relieved entirely	32	88.8	13	56.5	7	63.6
Relieved largely	3	8.3	6	26.0	4	36.4
Relieved slightly	1	2.8	2	8.7	0	0.0
Relieved not at all	0	0.0	2	8.7	0	0.0

The human uterus is a midline organ, but has a bilateral origin. The uterus is formed by the fusion of the Müllerian ducts. The mesenchyme or muscle fibers are laid down on each duct and the muscle fibers interdigitate at the line of fusion on the anterior and posterior walls of the uterus. The blood and nerve supply of the uterus is bilateral. In the uterus simplex, the fused mesial wall of the Müllerian ducts are resorbed in a caudocranial direction, and an arrest in the resorption of the fused mesial wall of the Müllerian ducts, at different levels leads to the uterus septate or subseptate.<sup>1</sup>

In the uterus duplex (rodentia), in which only the vagina represents a single midline birth canal, each uterus operates in labor as a single organ. However, some coordination between the two uteri is essential, for otherwise each uterus might expel a fetus into the vagina simultaneously, and produce a "traffic jam." This does not normally occur. In the bicornate uterus of the dog, for example, the lower portion of the uterus, which is analogous to the lower uterine segment of the human uterus, is fused. Thus, there must exist two types of coordinated activity in the uterus bicornis, namely, one to coordinate the activity between the two halves of the fused lower segment, and another between the fused lower segment and the two horns. If the first type of coordination did not exist, the two halves of the fused lower segment would not function simultaneously. If the second type of coordination did not exist, the two horns would empty simultaneously and the "traffic jam" would take place in the fused lower segment (corpus uteri). Thus, there exists in the anatomic bicornate uterus of the dog, a coordinating mechanism between the two fused halves and between the lower and upper (horns) segments. Thus, the two halves as well as the two segments of the uterus in the uterus bicornis are coordinated, at least during labor.

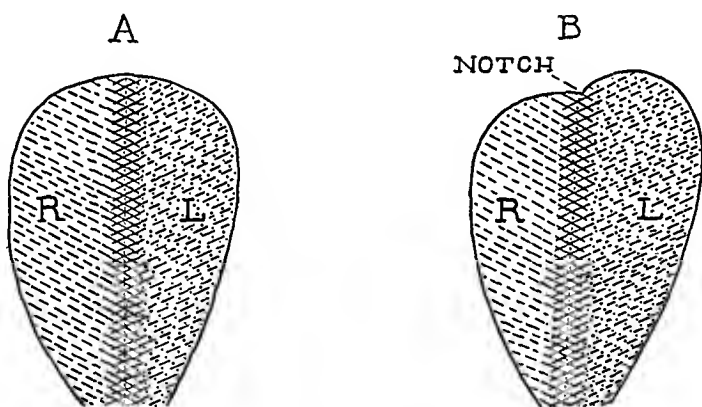


Fig. 1.—Schematic. A, Uterus with each lateral half (R and L) in equal tone. B, Uterus with left lateral half atonia (paresis or paralysis), while the right lateral half is hypertonic. Notch is the result of the change in tone of the two halves of the uterus at the mesial boundaries.

If ontogeny recapitulates phylogeny then the uterus simplex must possess the same coordinating mechanism, namely, one to coordinate the two halves and the other to coordinate the upper and lower segment. Observations on the uterus simplex of the monkey shows that such mechanisms physiologically exist, and must exist in order to prevent obliquity of the uterus or a sacculcation of the upper or lower segment, or one of the uterine quadrants. If the various quadrants of the uterus were not coordinated, obviously a uterine contraction would not occur evenly throughout the uterus, and the uterus could not contract in one quadrant and relax in another simultaneously.<sup>1-4</sup>

A disturbance of the physiology of the pregnant and parturient uterus may lead to difference in tone or strength of contraction of each lateral half of the uterus which would result in asymmetry. This will cause a lateral deviation of the uterus to one side of the abdominal cavity, which is called lateral obliquity of the uterus. A lateral obliquity of the

1. That adenomyoma becomes surgical at a later age than does pelvic endometriosis. This may be due to slower development of symptoms in the uterine site.

2. That the high incidence of fibromyomas and endometrial hyperplasia in our series would seem to add weight to a previously suggested common etiologic factor in these conditions and endometriosis.

3. That some disturbance of menstruation is the most commonly found symptom in our series. This takes the form of dysmenorrhea or some type of uterine hemorrhage.

4. That retroposition of the uterus was present in over half of our cases in which the position was noted.

5. That in external endometriosis the relief of symptoms was decidedly better accomplished by ablation of ovarian tissue than by conservative surgery.

6. That a much larger percentage of preoperative diagnoses are possible if attention is given to a more accurate history and if surgeons become as endometriosis minded as the incidence of the condition deserves.

7. That extensive endometriosis involving structures which render excision extremely hazardous, should be treated by removal of all ovarian tissue even in the younger age groups.

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## PSEUDOUTERUS ARCUATUS AND FUNCTIONAL MALFORMATIONS OF THE UTERUS

### THEIR EFFECT ON PREGNANCY AND PARTURITION

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CHANGES of contour in the normal pregnant and parturient uterus are encountered with sufficient frequency to warrant an inquiry into their significance. The textbooks of obstetrics make no reference to their mechanism or connotation during pregnancy and labor. A uterus arcuatus is a frequent malformation of the uterus. After labor the uterus returns to its normal contour. This type of uterus arcuatus is referred to as pseudouterus arcuatus and, with other temporary malformations of the uterus, is caused by a temporary incoordination of the uterus leading to functional malformations.



tion of the fundus uteri necessitates a differential diagnosis between a pseudouterus arcuatus and an anatomic uterus arcuatus. The intra-uterine pressure does not change with this type of functional malformation of the uterus. During the last trimester of pregnancy, a lateral half of the uterus may manifest tetany which necessitates a differential diagnosis of unilateral tetany, threatened rupture of the uterus, and abruptio placentae. I will present diagrams of pseudouterus arcuatus

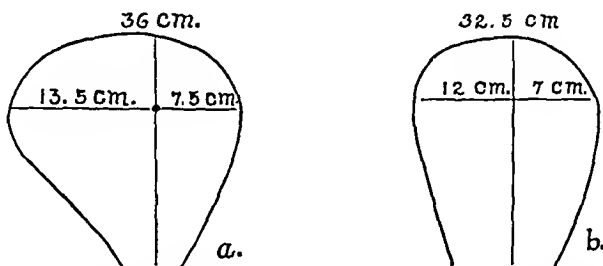


Fig. 2.—Right lateral obliquity of the uterus. *a*, Four weeks before the onset of labor. *b*, Two weeks before the onset of labor. With the onset of labor the uterus became symmetrical.

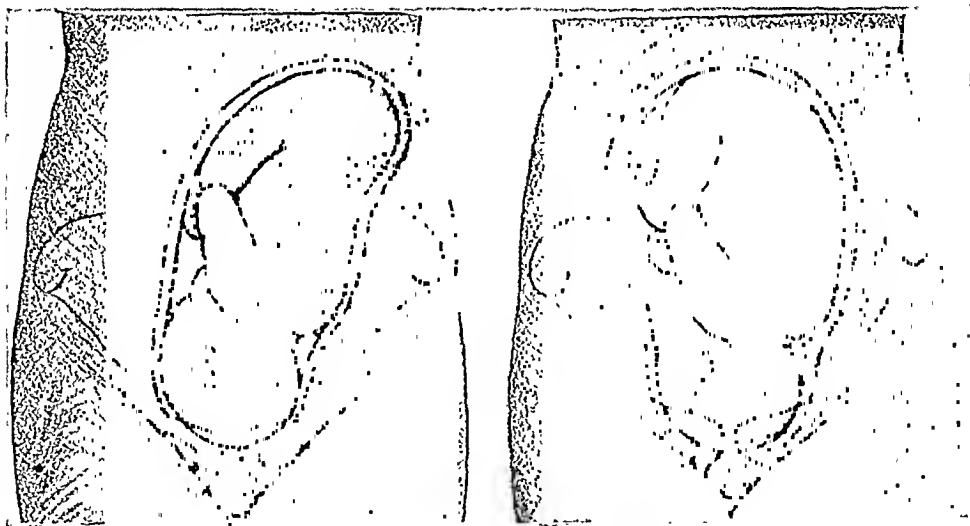


Fig. 3.—Uterus in left lateral obliquity and sacciform dilatation of the left upper quadrant of the uterus during the first stage of labor. With the second stage of labor the bag of waters was artificially ruptured which resulted in a normal functioning symmetrical uterus.<sup>1</sup>

and no case reports, because the labor in my cases terminated normally, and during involution no anatomic abnormality was found (Figs. 4, 5, 6, 7).

Sacculation is a pouching or ballooning-out of a portion of the uterus. An incoordination of one segment or one or more quadrants leads to compensatory contraction of the uterus of the other uterine segment or quadrants.

*Sacciform Dilatation.*—A ballooning-out of an upper or lower segment is frequently observed. I have presented a case with a marked sacciform dilatation of the upper left quadrant of the uterus in labor

uterus may be associated with a "notch" on its fundal surface (Fig. 1, B). The lateral half of the uterus in normal or exaggerated tone is firm at its mesial fundal limit, while the other lateral half of the uterus is markedly atonic or paretic which causes the fundal portion to rise upward and produce a "notch." This would cause one to suspect an anatomic uterus arcuatus.

Clinical observations on the changes of the contour of the pregnant and parturient uterus demonstrate numerous malformations to be functional. A frequent functional malformation of the uterus is one which causes us to suspect the existence of an anatomic uterus arcuatus. I refer to such a malformation as pseudouterus arcuatus, until it is actually proved to be anatomic rather than functional. Functional malformations of the uterus may be present during pregnancy, may persist during labor, or may appear only during labor. Anatomic malformations exist in the uterus before labor, may or may not disappear during pregnancy and labor, and return during involution. The presence in the nonpregnant state is the only criterion of the existence of an anatomic malformation.

The functional malformations of the uterus are as follows: (1) Pseudouterus arcuatus and lateral obliquity of the uterus; (2) sacculations of the uterus with the following types: (a) sacciform dilatation, (b) grosseesse angulaire, (c) Piskacek's sign; (3) irregular cervical dilatation.

Pseudouterus arcuatus is related to the lateral obliquity of the uterus. A lateral obliquity of the uterus is due to an incoordination of the uterus, resulting in atonia, paresis, or paralysis of a lateral half of the uterus, with a compensatory tonic contraction of the other lateral half of the uterus. The compensatory tonic contraction of a lateral half of the uterus is comparatively slight which permits the uterus to be deviated to either the right or left side of the abdominal cavity, but the fundus uteri presents a rounded outline, and is not "notched." The most frequent lateral obliquity of the uterus is to the right, but on frequent examinations of the contour of the uterus during pregnancy, will change to a normal midline symmetrical pregnant uterus, or to a left lateral obliquity of the uterus, or may return from the normal or left lateral obliquity of the uterus to a right lateral obliquity of the uterus. The intrauterine pressure does not change with the obliquity of the uterus. The lateral obliquity of the uterus may disappear with the onset of labor, or may persist for various periods of the labor (Figs. 2 and 3).

The pseudouterus arcuatus is usually associated with a lateral obliquity of the uterus. This functional malformation is due to the presence of a "notch" corresponding to the mesial aspect of the fundus uteri. The "notch" is caused by a marked tonic contraction of the upper portion of a lateral half of the uterus and an atonia, or paresis, or paralysis of the upper portion of the other lateral half of the uterus. In addition to the "notch" a vertical furrow may be palpated or seen on the upper mesial surface of the anterior uterine wall, extending downward from the "notch" for a short distance. The degree of changes of tone of the fundal portions of both lateral halves of the uterus will determine the degree of the pseudouterus arcuatus. The configura-

Shaw<sup>5</sup> reports a case that may be a bilateral ballooning of the fundus uteri. This occurred in a primipara, three months pregnant, in whom a cystic tender swelling was discovered on the upper portion of the uterus about the size of the uterus. The patient was laparotomized. The swelling proved to be a thin-walled sac of the uterine wall, and its cavity communicated with the uterine cavity by an opening which admitted two fingers. Both sac and uterine cavity were lined by the fetal membranes, and the fetus moved freely from one cavity to the other. This pathology appears to the author to have been a paresis of the upper portions of the lateral halves of the uterus, with the opening between the two uterine cavities as a tonic contraction of the physiologic retraction ring. The contents of the cystic and uterine cavities were removed, and the incision in the cystic cavity was sutured. The patient was laparotomized at a later date, the cystic cavity was not present, but a normal nonpregnant uterus was found. Bride<sup>6</sup> described a similar case.

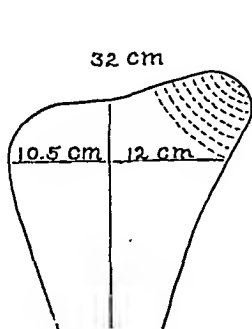


Fig. 6.

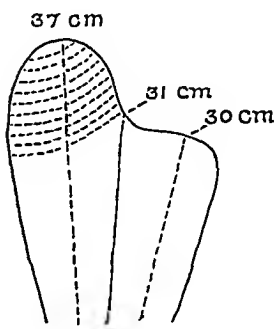


Fig. 7.

Fig. 6.—Contour of the uterus two weeks before the onset of labor. With the onset of labor the uterus became symmetrical.

Fig. 7.—Gravida II, para I. First pregnancy showed no asymmetry of the uterus. Two weeks before the onset of labor the uterus showed a slight right lateral obliquity and a sacciform dilatation of the upper right quadrant of the uterus. With the onset of labor the uterus was found symmetrical.

Grossesse angulaire is considered to be due to the implantation of the fertilized ovum high in the cornual extremity of the uterine cavity. The placenta brings about the angular form of the uterus. I am of the opinion that the location of the placenta plays no role in grossesse angulaire, but is primarily due to a sacculation of an upper portion of a lateral half of the uterus. The angular form of the uterus is frequently found in the first four months of pregnancy. It corrects itself, and is followed by a normal pregnancy and labor.

On our service, we have seen two interesting cases of grossesse angulaire. The diagnosis was made of a grossesse angulaire, but on account of the severe pain on the side opposite to the sacculation the question arose as to a possible ruptured ectopic gestation. The two patients were laparotomized and an angular formed pregnant uterus was found. The abdomen was closed. The postoperative course was normal. The pain subsided with no other treatment than the use of sedation. Subsequent examination disclosed a symmetrical pregnant uterus. I have observed a number of similar cases of grossesse angulaire with severe pain on one side which on sedation disappeared and was followed by a subsequently normal pregnancy and labor (Fig. 8).

Piskacek's sign is interpreted by the author to be a mild type of sacculation of the upper portion of a lateral half of the uterus. It is not related to the presence of the placenta. I believe that it is a mild type of grossesse angulaire.

diagnosis between  
 arcuatus. The intra  
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 pseudouterus arcuatus

which persisted throughout the first stage of labor, but with the rupture of the membranes in the second stage of labor the sacciform dilatation disappeared and the uterus became symmetrical<sup>1</sup> (Fig. 3).  
 Sacculation of the lower pole of the uterus is frequently encountered in which the "obstetric" cervix uteri is found deep and posteriorly. The

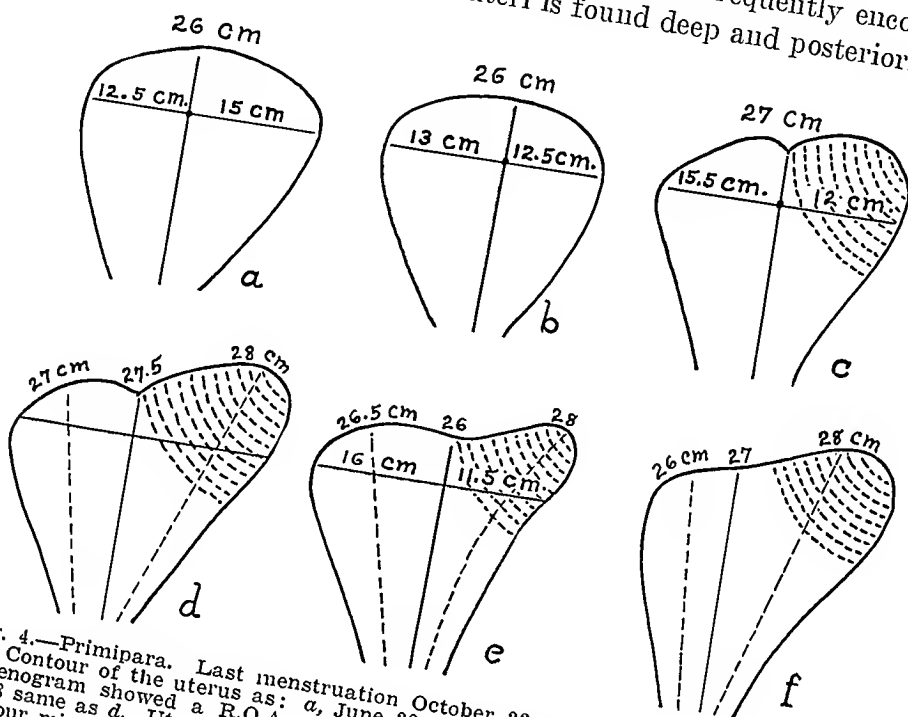


Fig. 4.—Primipara. Last menstruation October 22, 1930. Expected labor July 29, 1931. Contour of the uterus as: *a*, June 22. *b*, July 8. *c*, July 14. *d*, July 22, and July 28 same as *d*. Uterus remained as *f* throughout the labor of seventeen hours and forty-four minutes. Delivery by outlet forceps and episiotomy.

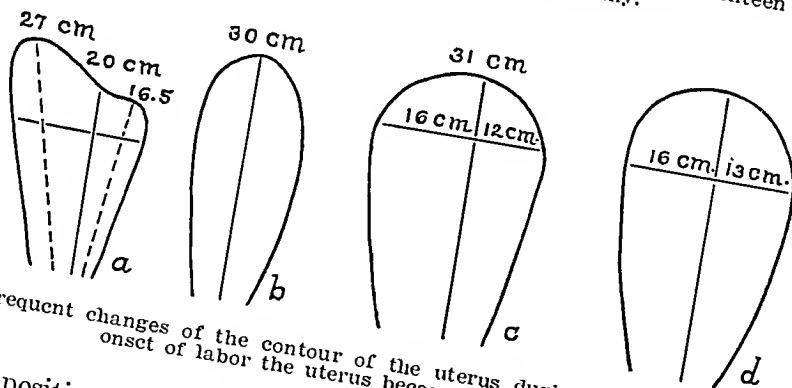


Fig. 5.—Frequent changes of the contour of the uterus during pregnancy. With the onset of labor the uterus became symmetrical.

posterior position of the "obstetric" cervix uteri and the ballooning-outward and forward of the lower pole of the uterus are due to a bilateral paresis of the anterior portions of the posterior portions of the uterus with compensatory contraction of the lower lateral halves of the lower pole of the uterus. This explains the sacculation of the cervix uteri.

I have not kept statistics on functional malformation of the pregnant or parturient uterus, but am of the opinion that some form of functional malformation of the uterus may be found in nearly all pregnant patients, if the contour of the uterus is frequently looked for.

#### MANAGEMENT OF FUNCTIONAL MALFORMATIONS

The evidence presented demonstrates that these functional malformations are due to a disturbance of the physiology of the uterus. We have no means whereby we can correct this pathologic physiology of the pregnant and parturient uterus. Our management is empirical. An appreciation of the mechanism and the fact that the malformation is frequently self-limited indicates intelligent expectancy. Rupture of the uterus has not occurred in my experience in any form of functional malformation, and from a physiologic consideration, we need not fear this complication. Neither should we fear malposition and malpresentation. The treatment is governed by the conditions that actually arise.

#### CONCLUSIONS

1. The human uterus is a bilateral organ embryologically, anatomically, and physiologically.
2. The human uterus manifests bilateral synchronous and coordinated function.
3. Some degree of incoordination of each half of the uterus is not infrequently present during pregnancy and labor.
4. Pseudouterus arcuatus is due to an incoordination of the two halves of the uterus. The true or anatomic type of uterus arcuatus can be definitely diagnosed only post partum.
5. Lateral obliquity of the uterus is due to an incoordination of the two halves of the uterus.
6. Sacculation is due to a disturbance of a part of the upper or lower portion of each lateral half of the uterus.
7. Irregular cervical dilatation is explained on the basis of the incoordination of the two lateral halves of the uterus.
8. The management of functional malformations of the uterus is intelligent expectancy.

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*Irregular cervical dilatation* is frequently encountered, and is usually associated with a lateral obliquity of the uterus. The normal functioning parturient uterus is associated with a synchronous and symmetrical dilatation of the lateral lips of the external os. When the uterus manifests a lateral obliquity, the uterine contractions of the atonic lateral half of the uterus do not undergo the same anatomic physiologic changes as the other half of the uterus. This brings about an irregularity of cervical dilatation. Or, one-half of the uterus is in the first stage of labor, while the other half of the uterus is in the second stage of labor.

Functional malformations of the uterus in my experience do not cause malpositions or malpresentations. The change of the form of the uterine cavity does not bring about a change of the intrauterine hydrostatic pressure. The fetus possessing a fetal postural mechanism accommodates itself to the form of the uterine cavity; the fetal form or ovoid does not change. A longitudinal position and presentation will become

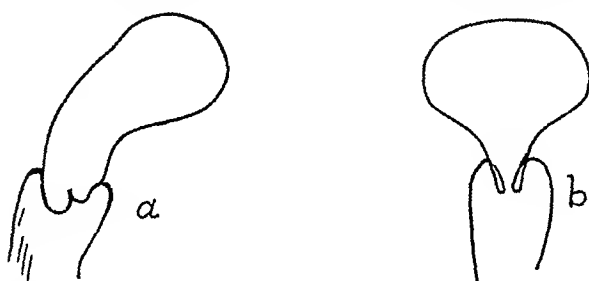


Fig. 8.—Multipara, pregnant about twelve weeks. Diagnosis: Grossesse angulaire and threatened abortion. Uterus in left lateral obliquity with marked tenderness on the right side. Twelve hours after the first examination the uterine colic subsided. Rectoabdominal examination showed a normal pregnant uterus. The pregnancy and labor which followed were normal.

more or less oblique, the presenting part may be high, or the presenting part may even rest in one of the iliac fossae, but the attitude of the fetus is not influenced by a functional malformation of the uterus. The author is convinced that a malposition or malpresentation results primarily from a disturbance of the fetal postural mechanism, but the mechanical factor plays a very minor role in these types of dystocia.<sup>7</sup>

#### THE DIAGNOSIS OF FUNCTIONAL MALFORMATIONS OF THE UTERUS

The presence of a "notch" on the fundal surface of the uterus, lateral obliquity of the uterus, sacculations, and irregular cervical dilatation during pregnancy and labor usually indicates a functional malformation of the uterus. If the malformation changes during pregnancy and labor, this change is practically pathognomonic of a functional condition. The presence of a "notch" on the fundal surface of the uterus per se does not indicate a diagnosis of uterus arcuatus. A "notch" is not characteristic of the uterus arcuatus of the monkey during labor. An abnormal contour of a lateral half of the uterus, or a segment of a lateral half of the uterus is characterized by a decrease in the tone of one-half or segment in comparison to the rest of the uterus by palpation. The contour of the uterus is transitory. The roentgenograms are of little value for the diagnosis. Only when the malformation persists post partum can the diagnosis of an anatomic malformation be made.

In this undertaking, I was encouraged by Dr. George E. Pfahler, Chairman of the Cancer Committee of the Philadelphia County Medical Society, by Dr. A. H. Estabrook of the American Society for the Control of Cancer, and by Dr. Ludvig Hektoen, Chairman of the Committee on Scientific Research of the American Medical Association. From this latter committee we received aid to cover the clerical expense of the Research.

My associates, Dr. Faith S. Fetterman, Dr. Margaret C. Sturgis, and I set about finding 1,200 white women thirty years of age and over who would volunteer to come for examination twice a year for five years. We transferred to this list our own patients who were already in the habit of coming for pelvic examination once a year. We transferred to the list patients from the postoperative follow-up clinic of the Hospital of the Woman's Medical College. We added to the list a few patients who consulted us for other than pelvic conditions and upon whom a routine pelvic examination was made. We recruited volunteers from women's clubs, from nurse alumnae associations, from social service organizations, and from the public at large as a result of the newspaper publicity given to the Research.

Each volunteer was given a leaflet describing the purpose of the research, stating that my associates and I had volunteered our services, and stating that if anything abnormal were discovered, a report would be made to her family doctor. In this connection, I should like to mention that the cooperation received from the family physicians has been most gratifying. While a few volunteers withdrew from the list stating that their doctors did not approve of this project, many more reported that their doctors were enthusiastically in favor of it.

As a result of the support that we have received from the volunteers and from their medical advisers, we are now in a position to report on the first and second examinations of a series of 1,000 women.

These examinations consisted in:

1. A careful bimanual pelvic examination
2. A careful inspection of the cervix in a good light
3. The application of Lugol's solution to the cervix according to the technique of Walter Schiller
4. The use of a blunt tipped pocket probe to detect friability of tissue according to the technique of Chrobak.

We did not use the colposcope, in the first place because we do not own one, in the second place because we wished to confine our tests to those that could be duplicated by the average general practitioner. At first quite a few biopsies were performed. As the experiment proceeded, we were more inclined to recommend the removal of cervical pathology in toto by means of surgery or conization.

In the first 1,000 examinations 4 malignancies of the uterus were found.

The first of these was in a woman 68 years of age. She had reported to Dr. Fetterman once a year for ten years for pelvic examination and had been transferred to the Research list. When she presented herself for examination she stated that she had noticed a spotting of blood for three days. The cervix was

## AN EXPERIMENT IN CANCER CONTROL\*

### PRELIMINARY REPORT ON PERIODIC PELVIC EXAMINATIONS OF ONE THOUSAND WELL WOMEN

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MARGARET C. STURGIS, M.D., PHILADELPHIA, PA.

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THE percentage of uterine cancer cases which really are cured may be said to vary inversely with the stage of the disease in which the patient receives treatment.

This is well shown by a series of 50 consecutive cancers of the cervix treated on the Gynecological Service of the Woman's Medical College Hospital during the years 1931 to 1935 inclusive.

TABLE I. FIFTY CONSECUTIVE CASES OF CANCER OF THE CERVIX

GRADE	NO. OF CASES	FIVE-YEAR SURVIVALS	PER CENT
I	26	16	61½
II	9	3	33
III	11	0	0
IV	4	0	0

Since the organization of the American Society for the Control of Cancer in 1914 and the formation of the Cancer Committee of the Philadelphia County Medical Society in 1927, the women of this city have been told in season and out of season what the early symptoms of cancer of the uterus are, and that they should immediately consult their family physician if such symptoms appear.

If the members of this Society who practiced gynecology in Philadelphia before 1914 will recall the patients with cancer of the uterus who presented themselves before that date and will compare them with the patients who present themselves today, I am sure all will agree that the campaign to "Fight Cancer with Knowledge" has accomplished wonders. Nevertheless, in spite of this educational campaign, 321 women died of cancer of the uterus in this great medical center last year.

A consideration of these facts leads to the conclusion that cancer of the uterus may run its course for a variable length of time without causing symptoms which attract the patient's attention and that, if discovered in this early stage, the results of treatment might be different. In the hope that it might be possible to detect cancer of the uterus in this early and symptomless stage or that it might be possible to detect and eliminate lesions which predispose to the development of cancer, I decided to test the method of periodic pelvic examination on a large series of women.

\*Read at a meeting of the Obstetrical Society of Philadelphia, January 4, 1940.



normal, and diagnostic curettage showed adenocarcinoma of the body of the uterus (Fig. 1). Since operation was contraindicated by various medical handicaps, radium and x-ray were used.

The second malignancy was found in a patient whom I had been asked to see on account of right upper quadrant pain. A routine pelvic examination showed a lacerated, hypertrophied, and eroded cervix. The Schiller test was negative. The probe sank in at one corner of the erosion. From this area a portion was taken for biopsy. In this tissue, Dr. Ingleby and Dr. Geiss found a small area of squamous cell carcinoma (Fig. 2). Radium and x-ray were used.

One of our volunteers asked that her mother and sister might be added to our list. The sister was found to have an extensive papillary erosion of the cervix which I excised by means of the Sturmdorf technique. I was surprised to receive word from the laboratory that a small area of squamous cell carcinoma had been found in the tissue removed (Figs. 3 and 4). Radium (4,050 mg. hours) was used.

A fourth woman came with a group of club women from a near-by suburb. Examination showed an extensive papillary erosion which was excised by the Sturmdorf method. Again to my surprise, Dr. Ingleby and Dr. Geiss discovered a small area of squamous cell carcinoma in the erosion (Fig. 5). Radium (3,900 mg. hours) was used.



Fig. 5.—Squamous cell carcinoma of cervix discovered in papillary erosion removed by Sturmdorf trachelectomy. (W. C. H. 45989.)

In addition to these early malignancies, 357 benign lesions were found in 318 volunteers. These comprised:

Papillomas	1
Leucoplakic areas	6
Polyps	43
Endocervicitis and cervicitis	48
Inflammatory erosions	189
(Simple 50, papillary 53, follicular 1, not specified 85)	
Myomatous tumors	66
Ovarian cysts	4



Fig. 1.



Fig. 2.

Fig. 1.—Curettings showing adenocarcinoma of the body of the uterus. (W. C. H. 43557.)

Fig. 2.—Squamous cell carcinoma of cervix found in tissue removed by biopsy. (W. C. H. 43433.)



Fig. 3.

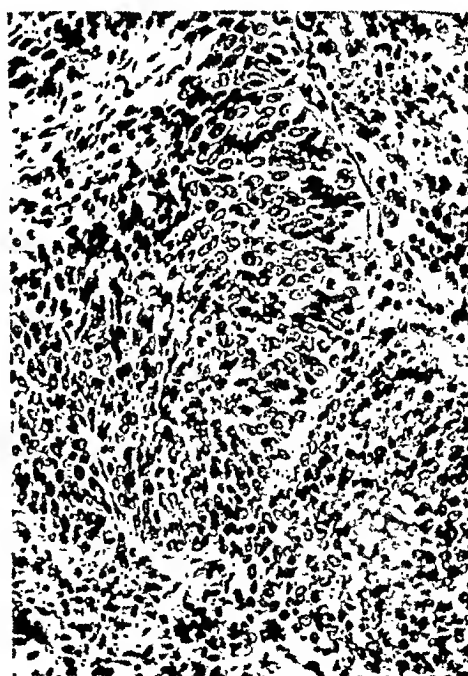


Fig. 4.

Fig. 3.—Squamous cell carcinoma discovered in a papillary erosion of cervix removed by Sturmdorf trachelectomy. (W. C. H. 46027.) (Low power.)

Fig. 4.—Squamous cell carcinoma of cervix discovered in papillary erosion removed by Sturmdorf trachelectomy. (W. C. H. 46027.) (High power.)

## DISCUSSION OF ARTICLES ON PAGES 983 AND 995

DR. LEWIS C. SCHEFFEY.—It is noteworthy that in Dr. Macfarlane's series of 50 consecutive patients, 70 per cent were in Classes I and II. This is an unusually high percentage for anyone to see. In our experience, of nearly twenty years, from 1921 on, our Class I and II patients have ranged between 10 and 12 per cent.

She is to be congratulated on the unusually high five-year survival rate. The statistics she presents reveal no survivals in Classes III and IV, which means that it is the comparatively early case which makes up the reported survival rate of 38 per cent. Our salvage rate at Jefferson is about 16 per cent, all classes considered.

The four cancers discovered in the first 1,000 cases, and properly treated, have alone proved the value of Dr. Macfarlane's study. The recognition of benign lesions is of even more value, for I believe that the abnormal cervix predisposes to malignant change whatever may be the other factors concerned.

The plan of preliminary study outlined by Dr. Teahan and Wammock is complete and adequate. I am glad to see that the authors use the Schmitz classification. Anyone who has looked through Heyman's precise *Atlas*, relating to the League of Nations' classification of cervical cancer, will, I think, be carried away by the maze of detail encountered in attempting to follow it with accuracy. I would far rather talk to a colleague in the fairly simple terms of Schmitz, I, II, III and IV.

In our own work, we began with radium alone; later we used x-ray therapy after the radium. For the last three or four years we have been employing x-ray in the same dosage as Dr. Teahan, preliminary to the radium application. I am not, as yet, prepared to make any definite comparison regarding the use of preliminary x-ray prior to radiation with radium as compared with our former method. There are advantages and disadvantages. The advantages in using preliminary external radiation are that it will usually clear up the nasty, sloughing cervical lesion, reduce infection, and probably reach those cancer cells that are beyond the reach of radium used locally. However, it often happens that when one dilates the cervix afterward, preparatory to applying intra-uterine radium, he will find that underneath an apparently clean surface there is almost as much friability of the tissue as before the x-ray was administered. Also, the contracture which frequently results makes it more difficult to apply the radium in some instances.

The dosage of radium employed, about 8,000 mg. hr., with 1 mm. platinum screening, is a larger dose than we are giving at Jefferson. We limit our dosage to 3,600 to 4,500 mg. hr. dependent upon the extent of the lesion and the condition of the patient. Larger doses should theoretically be more effective, but we have experienced very severe reactions, local and general, from the larger doses.

I spoke about the fallacy of the five-year standard of survival. Recently I presented some interesting statistics from the Jefferson clinic which tended to show that a certain number of our survivors were living because of repeated radiation for recurrence, at varying intervals after the primary course of radiation therapy. Fifty-three per cent of the patients surviving from five to sixteen years had had a single course of radiation therapy, either with radium or x-rays, or a combination of the two, while 46 per cent had survived over an equal period because of repeated radiation therapy for recurrence at varying intervals after the primary course of treatment. Our survival rates are definitely influenced by re-radiations for recurrence, resulting from careful follow-up observations at regular intervals.

DR. CHARLES A. BEHNEY.—Cone irradiation has been employed by us for only fourteen months in treating about 30 cases. The cones vary in diameter to fit the vagina, and are similar to the cylindrical vaginal speculum except that they are made of lead-lined steel. They are circular, 50 cm. long, and fit on the x-ray tube so that the x-rays are delivered directly to the cervix without

Some form of treatment was recommended in 159 of these cases and was carried out in 113 cases. The procedures used were as follows:

Excision of leucoplakic areas	1
Excision of polyps	30
Cauterization of cervix	32
Conization of cervix	11
Surgical:	
Repair	7
Amputation	4
Sturmdorf	16
Not specified	7
Hysterectomy	5
Removal of ovarian cysts	2

Upon the second examination of these 1,000 volunteers, after an interval of six months, no malignancies were found. Old lesions were present in 177 women, 76 new lesions were found in 69 women. These new lesions comprised:

Leucoplakic areas	4
Polyps	15
Endocervicitis and cervicitis	19
Inflammatory erosions	24
(Simple 10, papillary 10, follicular 2, not specified 2)	
Myomatous tumors	14
Ovarian cysts	0

At this stage of our research, it is impossible to determine the real value of this undertaking. The first patient in whom malignancy was discovered would probably soon have found her way to a doctor whether she had come for periodic examination or not. The second case of malignancy might have lost some time before her doctor would have thought to examine her. The third and fourth malignancies had no pelvic symptoms except a moderate amount of leucorrheal discharge. It is highly probable that weeks or months would have elapsed before they reported this to their physicians.

The significance of the benign lesions which were discovered and the importance of treating them are debatable subjects upon which the pendulum of medical opinion has not yet come to rest. Since the earliest cases of cancer of the cervix that I have observed have always been found in areas of erosion or inflammation, I am of the opinion that these areas of chronic epithelial irritation predispose to the development of cancer. I, therefore, believe that the elimination of this type of cervical pathology is a wise and necessary procedure. I further believe that, in many cases, the only way to discover cervical pathology is by means of periodic pelvic examinations.

# A STUDY OF THE INCIDENCE OF SYPHILIS IN PREGNANT WOMEN AND SOME RESULTS OF THERAPY

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RECENTLY we made a determination of the incidence of syphilis in the patients seen at Duke Hospital. As a whole it was found to be 8.13 per cent. There was a marked disproportion between the white and colored patients. The incidence in white male patients was 2.7 per cent, and for the white female patients 3.2 per cent. In colored males the incidence of infection was 29 per cent and in the colored females 32 per cent. As can be seen from these figures, for the population group from which these patients were drawn, the incidence of syphilis in the colored race was roughly ten times that of the white race, and a greater incidence of syphilis was found in the females of both races. Because of this finding, we felt that a determination of the incidence of syphilis in pregnant women should be made because of its implications as a public health problem and as a problem of preventive medicine.

As a basis for this study the records of 2,152 unselected patients, all pregnant women, who were admitted during the years 1930 to 1938 to the obstetric wards, both private and public, of this hospital were examined.

The criteria employed for the diagnosis of syphilis consisted of either the laboratory finding of repeatedly positive blood serology and, in early seronegative syphilis, the finding of the *Treponema pallidum* on repeated dark-field examinations, or a definite history of syphilis for which no treatment or inadequate or insufficient treatment had been received with or without physical signs or stigmas of syphilis.

Blood serologic examinations were made routinely on all the obstetric patients at the time of their first visit to the prenatal clinics or at the time of their admission to the hospital, if no prenatal examinations had been made, and also in most cases serologic examinations were again made at the time of delivery. The serologic tests used were the Wassermann and Kahn reactions.

All of the patients diagnosed as having syphilis in the group on which this study was based were found to have a strongly positive Wassermann and/or Kahn reaction with the exception of 9 cases. Of these 9 serologically negative cases, 8 of the patients gave a definite history of syphilis and of having received some treatment prior to their pregnancy and 1 patient had dark-field, positive, seronegative, primary syphilis.

## DATA

Of the 2,152 pregnant women whose case histories were studied, we found that 1,249 were white and 903 were colored. The incidence of syphilis in this group as a whole was 7.66 per cent as compared with an incidence of 8.13 per cent for the hospital patients as a whole. Only 10 cases of syphilis were found in the white group or an incidence of 0.8 per cent; whereas in the colored group, 155 patients

passing through any intervening tissues. We have employed these in a small number of cases for only one year, and are unable to report results except to say that the immediate effect seems to be good, particularly in the advanced cases where one may be unwilling to apply radium locally.

May I add a word of appreciation for the first paper. We have known of this work for some time but until tonight were ignorant of the details and the result of this work at the Woman's Medical College Hospital. It emphasizes the need for greater stress on early diagnosis of carcinoma by frequent biopsy, both in our clinical practice and in our teaching. It is my conviction that further improvement in end results will be realized in this direction rather than by changes in therapeutic technique.

DR. HELEN INGLEBY.—I have here a diagram of a section of cervix showing an area of atypical cells with numerous mitoses, but no infiltration. Is this carcinoma? Further experience may give us the answer. This is not the same thing as a precancerous lesion. By a precancerous lesion is meant an area of cell proliferation, usually of inflammatory origin, which forms a suitable site for malignant growth. Growth may or may not supervene in a given case, but removal of such sites will probably prevent most if not all carcinomas in the cervix. Dr. Macfarlane in common with the majority of clinicians and pathologists holds that squamous or basal cell carcinoma of the cervix always arises in a previously diseased area. If she and they are right it follows that epithelioma of the cervix is preventable, not only in the majority, but in all cases.

DR. WAMMOCK (closing).—I wish to call your attention to the fact that of the histories of 229 cases which we have reviewed with reference to symptomatology, 80 per cent had bleeding in some form, leaving a total of 20 per cent without any bleeding. Of this number, some six per cent had advanced cancer before any sign or symptom appeared. During the year 1937, we discovered three Stage I cases by the use of the Schiller technique, referred to by Dr. Macfarlane. However, we do not rely solely upon this test. It is used as an adjunct to routine pelvic examination. Likewise, we do not use the colposcope.

As to the clinical grading, we prefer Schmitz' classification, which seems to be a very simple method. With reference to the dosage of radium in early cases, we feel that a large dose should be delivered if one expects to completely eradicate the cancer.

DR. TEAHAN (closing).—It must not be forgotten that the good results first obtained by irradiation in carcinoma of the cervix were obtained with radium alone. Theoretically, x-ray should be of value, for by its use more radiation reaches the broad ligaments. Practically, it is of value in some patients in cleaning up infection and making it easier to find the cervical canal.

Regarding re-irradiation with radium, with our dosage we practically never apply radium the second time.

DR. MACFARLANE (closing).—We have used the Schiller test systematically in our 2,000 examinations but feel that we have not derived much help from it. In fact, my associates and I feel that we derive as much help from a careful inspection of the cervix without Lugol's solution as with it.

have been shown. In Table IV we have shown the terminations of pregnancy in 21 patients who received *some treatment both before and during pregnancy*. And in Table V the terminations of pregnancy have been tabulated in 5 patients who, we believe, had had some treatment, but about whom we could not obtain accurate information as to the amount or type of therapy.

TABLE I. THE TERMINATION OF PREGNANCY IN 56 SYPHILITIC WOMEN WHO RECEIVED NO ANTISYPHILITIC THERAPY BEFORE OR DURING GESTATION

ABORTIONS	MISCARRIAGES	PREMATURE	STILLBIRTHS	FULL-TERM LIVE BIRTHS
0	1	20	5	30
0	1.8%	35.7%	8.9%	53.6%

TABLE II. THE TERMINATION OF PREGNANCY IN 17 SYPHILITIC WOMEN WHO RECEIVED SOME ANTISYPHILITIC THERAPY BEFORE BUT NONE DURING GESTATION. AVERAGE AMOUNT OF THERAPY 3.1 GM. ARSPHENAMINE AND 0.5 GM. HEAVY METAL

ABORTIONS	MISCARRIAGES	PREMATURE	STILLBIRTHS	FULL-TERM LIVE BIRTHS
0	0	2		15
0	0	11.8%		88.2%

TABLE III. THE TERMINATION OF PREGNANCY IN 66 SYPHILITIC WOMEN WHO RECEIVED SOME TREATMENT DURING PREGNANCY ONLY. AVERAGE AMOUNT OF THERAPY 1.75 GM. ARSPHENAMINE AND 0.3 GM. HEAVY METAL

ABORTION	MISCARRIAGE	PREMATURE	STILLBIRTHS	FULL-TERM LIVE BIRTHS
0	0	5	1	60
0	0	7.6%	1.5%	90.9%

TABLE IV. THE TERMINATION OF PREGNANCY IN 21 SYPHILITIC WOMEN WHO RECEIVED SOME TREATMENT BEFORE AND DURING PREGNANCY. AVERAGE AMOUNT OF THERAPY 4.3 GM. OF ARSPHENAMINE AND 1.4 GM. HEAVY METAL

ABORTIONS	MISCARRIAGES	PREMATURE	STILLBIRTHS	FULL-TERM LIVE BIRTHS
0	0	0	0	21
0	0	0	0	100%

TABLE V. THE TERMINATION OF PREGNANCY IN 5 SYPHILITIC WOMEN WHOSE THERAPY, IF ANY, WAS NOT KNOWN TO US

ABORTIONS	MISCARRIAGES	PREMATURES	STILLBIRTHS	FULL-TERM LIVE BIRTHS
		1	1	3

At the top of each table we have shown the average amount of treatment received by each group to whom antisypylitic therapy was administered. These figures have been expressed as grams of arspnenamine and grams of heavy metal as determined by totaling the amounts received by each individual patient and then, by dividing by the total number of patients in each group, a general average was obtained. The therapy was expressed in this form for simplicity because, as

were diagnosed as having syphilis, giving an incidence of 7.6 per cent. The ages of these 165 patients found to have syphilis ranged between 16 and 42 years. Only 60 of them were primiparas. Most of them were from the lower economic brackets. The diagnosis of latent syphilis was made in 154 of the patients. Sero-negative primary syphilis was diagnosed in 1 patient and 6 of the patients were found to have secondary syphilis. Prenatal syphilis was diagnosed in 3 of the patients. One patient was found to have central nervous system syphilis.

Only 87, or 53 per cent, of the 165 patients received any antisymphilitic treatment during their gestational periods, and only 19, or 21 per cent, of the 87 partially treated patients received near the minimal amount of therapy which has been shown by the clinical cooperative studies<sup>4</sup> to be necessary for the prevention of prenatal syphilis in the offspring of infected mothers. Of the 87 partially treated patients, 68, or 79 per cent, did not present themselves for diagnosis or treatment of their syphilis until after the sixth month of gestation. In 56 of the group of 165 syphilitic patients, the diagnosis of syphilis was not made until the patients were admitted to the hospital, usually in the first stages of labor. For various reasons, the remaining 22 patients in the group of 165 syphilitics failed to receive antisymphilitic therapy during their gestational period, or if some of them did receive treatment, we have no accurate statements in our records showing the time or amounts of such therapy.

Admittedly this group of patients constituted too small a number to allow the drawing of any definite conclusions as regards the true value of prenatal antisymphilitic therapy in the protection of offspring from infected mothers such as other investigations have shown it to be.<sup>1-5</sup> It was thought, however, that we could show by our studies that if some antisymphilitic treatment were given during pregnancy, and even though late in pregnancy and in amounts inadequate as compared to the amounts recommended by the clinical cooperative group studies,<sup>4</sup> a more favorable termination of the pregnancy would result. It was observed that more full-term live births occurred in a group of patients who received some treatment during pregnancy than were found to occur in a group of patients who received no treatment, or who were inadequately treated prior to pregnancy. This concept has been expressed before in the writings of Moore,<sup>1</sup> McCord,<sup>3</sup> Turner and McKelvy,<sup>6</sup> Mitchell,<sup>7</sup> and by Cole and others in the cooperative clinical studies,<sup>4</sup> and perhaps by others.

We recognized that most of the patients studied had latent syphilis, and that many were also multiparas; both of which conditions have been shown<sup>1, 2</sup> to play favorable roles in allowing full-term live births to occur even though the child so born may have prenatal syphilis. We were, however, dealing with similar patients in all the groups into which we had divided our patients for purposes of statistical classification, and since the terminations of pregnancy were so much better in those patients who received some treatment as compared with the untreated cases, we could not help but feel that the treatment caused these results.

This observation has been illustrated by dividing the patients into 5 groups with the results of the pregnancies being tabulated in Tables I, II, III, IV, and V. The terminations of pregnancies in 56 patients who received *no treatment either before or during pregnancy* have been shown in Table I. Table II was made to illustrate the terminations of pregnancy in 17 patients who *received some treatment before pregnancy, but none during pregnancy*. In Table III the terminations of pregnancy in 66 patients who *received some treatment during pregnancy only*



legislation. Recent laws have been passed requiring physical examination and serologic tests for syphilis of both partners prior to marriage.\* A law which went into effect on Jan. 1, 1940 also requires all pregnant women to have a Wassermann or other approved serologic examination made.† If syphilis is diagnosed, treatment is mandatory.‡ Only future observations can show the true value of these laws. It would be of interest to study a similar group of patients within the next few years in this community to see if the recently enacted laws of this state will further the prevention of syphilis in unborn children as is expected of them.

#### SUMMARY AND CONCLUSIONS

1. The incidence of syphilis was found to be about one-fourth as great in the white and colored obstetric patients as it was found to be in the white and colored women patients admitted to the hospital wards and seen in the out-patient clinics of those departments other than obstetrics.

2. The incidence of syphilis was found to be roughly ten times greater in the colored women than in the white women both in the pregnant and nonpregnant groups.

3. More full-term live births were found to occur in the group of syphilitic mothers who received some antisyphilitic treatment, even if given late in pregnancy and in inadequate amount, than were found to occur in instances of pregnancy in the groups of syphilitic women who had received no treatment or who had been inadequately treated prior to pregnancy.

4. Most of the patients in our study were diagnosed as having syphilis late in their pregnancy, and consequently, antisyphilitic therapy was in most instances inadequate from the standpoint of preventing prenatal syphilis in their offspring by present accepted standards.<sup>1, 2, 4</sup>

5. More effort should be made towards getting pregnant women to physicians for prenatal care during earlier periods of gestation than most of our patients presented themselves.

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\*Senate Bill 121: "An Act to Require Physical Examination Before Issuance of License to Marry," Public Laws of North Carolina, Regular Session 1939, Chapter 314.

†Senate Bill 120: "An Act to Further the Prevention of Syphilis in Unborn Children in North Carolina by Requiring Blood Test Examination of Prospective Mothers," Public Laws of North Carolina, Regular Session 1939, Chapter 313.

‡Venereal Disease. Part I. Control and Treatment, Articles 7191 to 7198, North Carolina Code Annotated.

previously stated, we have not attempted to show the value of prenatal antisyphilitic therapy from the viewpoint of preventive medicine, therefore exact qualitative and quantitative expression of therapy has not been deemed necessary for our purpose. The arsenicals used were either arsphenamine or neoarsphenamine. The heavy metal was in nearly every instance bismuth of the insoluble form, as bismuth subsalicylate. The patients treated at clinics other than in this hospital may have received some mercury.

#### COMMENT

Certainly, the marked disproportion as found in the incidence of syphilis in female hospital patients as a whole as compared with the incidence found in obstetric cases is of some significance. Just how to explain this we do not know. One possible explanation of this observation may be that patients infected with syphilis are often at the same time infected with gonorrhea, and as is well known, gonorrhea frequently has disastrous effects on the female reproductive system with sterility as its aftermath. We have no statistics at present to support such a supposition, but hope later to attempt such a correlation. The social factor of marriage also must play some part in producing this disproportion.

The finding of a much higher incidence of syphilis in the colored women as compared to the white has been mentioned before by McCord.<sup>5</sup> We believe this is a generally accepted observation. The reasons for this are probably many, such as economic status, social habits, environment, and racial habits. All of these factors are far too complex to go into in a paper of this type.

If our records are any indication of the general status of prenatal antisyphilitic treatment at other clinics, and if the prenatal treatment of syphilis is to assume its role as an ideal example of preventive medicine, an effort must be made to get pregnant women to physicians for prenatal care much earlier than most of our patients presented themselves. All that will be accomplished, otherwise, with inadequate prenatal antisyphilitic therapy, such as our patients received, will be to cause more pregnancies to terminate at full term with live births and thus probably to increase the number of prenatal syphilis occupying their place in our already burdened social structure. In support of this idea that the late and inadequate treatment of pregnant syphilitic mothers may increase the number of children with prenatal syphilis, we found after examination of the records of 35 such children who have been receiving antisyphilitic therapy in the Pediatric Clinic of this hospital that 37 per cent of these patients were born of mothers who had received insufficient treatment late in their pregnancies. It is recognized that prenatal syphilis in itself is not hopeless from a therapeutic viewpoint, but when one sees the difficulty usually experienced in getting the mothers of these patients in for adequate treatment of their syphilis, and with the same recognized difficulty with their offspring, the picture does assume a rather foreboding atmosphere. At present in North Carolina attempts to prevent such a miscarriage of therapeutic endeavor are being made by appropriate

Finally, the cancer treatment may be improperly planned or executed. An incomplete operation may be performed, the correct diagnosis not having been made, or the extent of the disease not having been appreciated. When one is in doubt as to the amount of radiation to use, there is a strong tendency to use an insufficient amount.

During the past ten years, 1928 to 1937 inclusive, a total of 229 cases of carcinoma of the uterine cervix have been observed at Jeanes Hospital. Of this number, 136 patients seen before Dec. 1, 1934, have been observed for five years or more, and it is with these that we propose to deal. All patients have been followed. A total of 118 patients had microscopic verification. Of the remaining 18, some made only one dispensary visit, and in other instances treatment was considered inadvisable because of the extent of the disease or the patient's general condition. None of these 18 patients survived five years.

It is our practice to make a thorough physical examination on all patients. When carcinoma of the cervix is suspected, the patient is anesthetized, a bimanual pelvic examination is made, the cervical canal dilated, the depth of the uterus determined, and the presence or absence of pyometra noted. A biopsy specimen is taken, and finally a bimanual rectal examination is made. Cystoscopy examination is made on all patients, and where symptoms or extent of the disease suggest ureteral blocking, the ureters are catheterized. An x-ray examination of the lungs, lumbar spine, and pelvis is routine.

The lesion is classified clinically according to Schmitz.<sup>1</sup> One is not always satisfied by the classification given an individual patient because of difficulties encountered in estimating the exact extent of the disease. The 136 cases observed are classified in Table II. Of the three Stage I

TABLE II. CLINICAL STAGES

	CASES	PER CENT
Stage I	3	2.2
Stage II	10	7.3
Stage III	42	30.9
Stage IV	81	59.6
Total	136	100.0

patients, one was discovered following hysterectomy for a fibromyomatous uterus, and one also had cancer of the breast. From the figures in the table one notes that nearly 60 per cent fall into the advanced group, Stage IV. Another 31 per cent fall into Stage III, leaving less than 10 per cent in Stages I and II. It will be noted that no Stage V cases are listed. They are included in Stage IV due to our inability to determine whether the disease was recurrent or, what was more likely, had never been primarily controlled.

Table III shows the distribution of the patients according to the histologic type of the cancer cell found. Squamous and anaplastic types are the most common, constituting 75 per cent.

Except as above noted, our treatment has been exclusively by radiation. Until 1933, the radium radiation was patterned after Heyman's method of small doses repeated once or twice at two- to three-week in-

# RESULTS OF TREATMENT IN CARCINOMA OF THE UTERINE CERVIX\*

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THE uterine cervix is accessible for diagnosis and treatment. No other region tolerates more radiation. In spite of these favorable factors, the results obtained in the treatment of cervical cancer are poor. What is the explanation of this paradox? Many factors are involved, but there can be no doubt that the extent of the disease when cancer treatment is undertaken has more to do with the ultimate result than anything else. Until more women will cooperate and have periodic pelvic examinations, the extent of the disease when the patient begins treatment will probably be found to be affected more by the length of the interval between the appearance of the first symptom and the institution of cancer treatment than by any other single factor. Table I indicates the delay in 167 patients whose histories contain this information. From this it appears that, while the patient with carcinoma of the cervix is consulting a physician more promptly, there is still an average delay of two months between the time she visits her doctor and the time of her first pelvic examination. Failure to make a correct diagnosis after pelvic examination is generally due to a satisfactory biopsy not having been made. The delay between the pelvic examination and the beginning of cancer treatment has been found to be due to an incorrect diagnosis, disbelief on the part of the physician that cancer is curable, and unwillingness of the patient to face the facts and submit promptly to the necessary treatment.

TABLE I. AN ANALYSIS OF 229 CASES, 1928-1937

This shows the average time between the initial symptom, first examination, and specific cancer therapy, using 167 cases in which these data were included in the history. This material was assembled for an unpublished report by B. E. Wright, M.D., Jeanes Hospital, Philadelphia, Pa.

YEARS	NUMBER OF PATIENTS	TIME IN MONTHS		
		ONSET TO FIRST — VISIT —	FIRST VISIT TO FIRST EXAMINATION	FIRST EXAMINA- TION TO FIRST TREATMENT
1929-1931	29	7.76	0.58	4.06
1932-1934	55	5.73	2.84	3.51
1935-1937	83	4.57	1.88	3.41
Average	167	5.55	2.0	3.6

As far as the cancer itself is concerned, there are variable factors. It may be very virulent or radioresistant. The patient may have associated conditions such as diabetes, syphilis, fibroids, or pelvic inflammatory disease, which makes treatment more difficult.

\*Read at a meeting of the Obstetrical Society of Philadelphia, January 4, 1940.

TABLE V. FIVE-YEAR SURVIVALS, DISTRIBUTION ACCORDING TO CLINICAL GRADES\*

	PATIENTS TREATED	FIVE-YEAR CURES	PERCENTAGE
Stage I	3	2	66.7
Stage II	10	6	60.0
Stage III	42	16	38.1
Stage IV	81	2	2.5
Stages I-IV	136	26	19.1

\*This table includes the Stage I patient treated by hysterectomy.

50 per cent chance for cure, whereas Stages III and IV have about 15 per cent chance for cure. The five-year results are given in Table VI. Of a total of 136 patients seen, 122 were treated and 26 survived five years or more. The absolute cure rate is 19.1 per cent and the relative cure rate 21.3 per cent.

TABLE VI. FIVE-YEAR SURVIVALS

Total cases seen	136
Alive five years	26
Absolute cure rate	19.1%
Total cases with microscopic verification	118
Alive five years	26
Cure rate	21.1%
Total cases treated	122
Alive five years	26
Relative cure rate	21.3%
Total cases receiving primary treatment	69
Alive five years	23
Cure rate	33.3%
Total cases treated by combined x-ray and radium	51
Alive five years	19
Cure rate	37.3%
Total cases receiving secondary treatment	53
Alive five years	3
Cure rate	5.7%

Our total number of cases includes a large number of patients who have received treatment for cancer before coming to us, and we have therefore seen fit to separate these from those in whom we initiated the treatment. In 69 patients the treatment was instituted by us, and the five-year cure rate in this group is 33.3 per cent. Fifty-three patients had received treatment for cancer elsewhere, the disease either not having been controlled or having recurred. These patients were given more treatment, but only three survived five years, i.e., 5.7 per cent.

Not all patients have received combined x-ray and radium therapy. In some of the advanced (Stage IV) cases the use of radium appeared to be contraindicated. A total of 51 patients received the combined x-ray and radium, and the five-year cure rate in this group is 37.3 per cent. In this group, two patients developed vesicovaginal fistulas, one following Heyman's technique and the other following the Regaud method. Four fistulas occurred among patients receiving an incomplete

TABLE III. HISTOLOGIC TYPES OF CANCER

	CASES	PER CENT
Squamous	49	41.5
Anaplastic	39	33.0
Basal	18	15.3
Adeno	12	10.2
Total	118	100.0

tervals to deliver a total of 6,600 mg. hr. of radium. This was followed by a course of high-voltage x-ray treatments. The x-ray factors have remained constant and are as follows: 200 kv., 50 cm. STD, 30 ma., 2 mm. Cu and 1 mm. Al filtration, four ports, two anterior and two posterior, fields 15 by 20 cm. A dose of 200 r. is delivered to each port three times a week for a total of 2,400 r. units to each port. At the beginning of 1933 the method of treatment was changed, x-radiation being given first. Immediately following completion of the x-ray treatments, radium is applied within the uterus in a rubber tandem consisting of three capsules of radium, two of 13.33 mg. and one of 6.66 mg. filtered with 1 mm. Pt, and intravaginally in a colpostat, one 13.33 mg. tube in each arm, and one 6.66 mg. tube in a rubber capsule filtered with 1.5 mm. Pt is placed in front of the cervix to deliver a total dose of approximately 8,000 mg. hr. The patient is anesthetized and the radium is applied but once. The bladder and rectum are protected by gauze packing, and an indwelling catheter is inserted in the bladder.

According to Arneson,<sup>2</sup> this method of applying radium results in the greatest amount of radiation reaching the broad ligaments of any which he studied. According to him, it delivers 7 T.E.D. to a point 3.3 cm. on each side of the cervical canal. However, Sandler<sup>3</sup> disputes Arneson's conclusions.

A comparative analysis of the two methods of application, even though the number of cases is small, will perhaps be of value. This is shown in Table IV. The apparent improvement may be ascribed to increasing

TABLE IV. CASES TREATED RADIOLOGICALLY\*

	CASES SEEN	CASES TREATED	5-YEAR CURES	ABSOLUTE CURE RATE	RELATIVE CURE RATE	AVERAGE R. TO TUMOR	AVERAGE MG. HR.
High intensity radium radiation and high voltage x-ray treatment (1928-1932)	82	72	14	17.0	19.4	2,380	4,671
High voltage x-ray treatment and protracted radium radiation (1933-1934)	53	49	11	20.7	22.4	3,115	6,346
Total	135	121	25				

\*The case treated by hysterectomy is not included.

dosage. The five-year survival as to the distribution of clinical grades is shown in Table V, indicating that Stages I and II have better than